Bulletin of

Cancer Progress

simple, effective, inexpensive

The usefulness of cytology in the diagnosis of cervical cancer has been well established. For example, the study in Memphis, Tennessee, covering the findings in 108,000 women who were examined, disclosed 393 intraepithelial carcinomas, of which 353, or 90 per cent, had not been suspected, and 373 invasive carcinomas, of which 112, or 30 per cent, were unsuspected. From the results of this and other studies, it seems obvious that cytologic tests should be made available to more patients.

Inasmuch as the evaluation of exfoliated cells is a highly specialized diagnostic service, periodic examination (case-finding) of the entire population is an enormous undertaking. There are, however, enough pathologists qualified in cytology in this country to make this useful adjunct to diagnosis available to every physician.

In addition to its effectiveness, two other aspects of the cytologic method make it extremely helpful to the physician. First, it is a simple office procedure and, second, it is inexpensive for the patient in terms of periodic health examination.

Cytologic evaluation is somewhat more complex, but is extremely useful, in the diagnosis of neoplasms of the lung and stomach. The effectiveness of the method for the detection of cancer in other sites is more equivocal. In any case, cytologic techniques afford a means for the diagnosis of cancer sufficiently early to increase significantly the probability of cure.

The best interests of the patient are served when the practicing physician who obtains the cellular material has close liaison with the pathologist who interprets the slide. False negative and false positive readings can best be detected as a result of close cooperation between the clinical physician and the pathologist who interprets the slides. The objective of adequate screening and cytologic reading cannot be accomplished by application of mail-order methods in large cytologic centers. The cellular material always represents an individual patient, and the problems of diagnosis and therapy must be applied to the patient on an individual basis. In all instances, close liaison between the pathologist and the physician can lead to an equitable solution of the individual problems.

Excerpted from "The Importance of Cytology to the Practicing Physician", a brochure prepared and distributed by the College of American Pathologists.

Cover—

Design by Don Smith, New York City.
Photomicrographs from the collection of Dr. G. N. Papanicolaou.

NEWSLETTER

SEPTEMBER-OCTOBER, 1960

The University of Chicago Argonne Cancer Research Hospital has a new accelerator which provides the most powerful electron beam available for the treatment of cancer in inaccessible areas without causing serious damage to adjacent organs. The unit employs a 16-foot-long tube which gives electron bursts of six ten-millionths of a second at the rate of 60 per second, and its power ranges from five to 50 million electron volts concentrated in a ray a half centimeter in diameter. Side effects of treatment with doses of radiation far higher than those used in conventional radiotherapy have been limited. The machine holds promise in the treatment of tumors in areas of the body previously difficult to reach with effective radiation because of the danger of damaging surrounding structures.

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In a report at the Sixth International Thoracic Congress in Vienna recently, Dr. John S. Harter (Univ. of Louisville School of Medicine) described a new, rapid technique for determining the presence of cancer cells in the circulating blood. The method, developed by Dr. Harter in collaboration with Drs. Bogdan Nedelkoff and William M. Christopherson, requires only one hour to perform. Blood samples are centrifuged in a mixture of polysorbate 80, polyvinylpyrrolidone and disodium ethylene diamine. The supernatant fluid is removed and the cellular elements are suspended in the same mixture with saponin added to hemolyze the red cells. Hemolysis is then stopped by the addition of calcium gluconate and the material is again centrifuged, filtered through a Millipore filter and stained by the Papanicolaou technique.

- - - - - - - - - - -

At the Eighth Congress of the Society of International Hematologists held recently in Tokyo, Dr. John B. Atkinson (Jefferson Medical College, Philadelphia) reported

promising results in his work with the use of bone marrow transplants to replace the destroyed bone marrow after radiation and chemotherapy in the treatment of leukemia and certain other malignant conditions. In the cases which he studied, Dr. Atkinson could determine that transplanted marrow was able to grow and spread, although this measure did not prevent fatalities from malignancy. If such bone marrow grafts can be successfully accomplished, it may become possible in the future to treat cancer by radiation and chemotherapy and then replace damaged bone marrow by means of transplants.

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The Chemotherapy Service of the National Cancer Institute is conducting studies on the use of pyrimidine analogues, 5-fluorouracil and 5-fluorodeoxyuridine, in the treatment of carcinoma of the colon and rectum. For inclusion in these new studies, the NIH is requesting physicians to refer their patients who have such lesions. In order to be accepted for the study, patients must be ambulatory, in good general condition and have tumor masses which can either be measured directly or demonstrated on roentgen films. Patients could be accepted if they have normal leukocyte counts, normal renal and hepatic function and if they have metastases in the lung, peripheral lymph nodes (such as supraclavicular or cervical) or skin. Physicians who desire to have their patients considered for the study should contact Dr. Clyde O. Brindley or Dr. Paul P. Carbone, National Cancer Institute, Bethesda 14, Maryland.

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The June 1960 issue of Cancer Research contains the Proceedings of a symposium on "The Possible Role of Viruses in Cancer" which was held in November 1959 at Rye, New York. Sponsored by the American Cancer Society, the symposium was one of a series of informal conferences being devoted to particular areas of research and limited to approximately 35 participants. The published Proceedings of this conference include formal papers and discussions, comments by certain of the participants and summaries of informal discussions which were prepared by presiding officers of the five different sessions.

(Continued after Page 180)

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B. AUBREY SCHNEIDER, Sc.D.

(1912-1960)

BYRON AUBREY SCHNEIDER was born on a farm in Frederick County, Maryland, on January 9, 1912. The next to the youngest of nine children, he spent his boyhood helping his family on the farm. When sixteen years old, he suffered a severe attack of rheumatic fever which left him with an enlarged heart and changed the course of his life. Instead of becoming a farmer, he went to Western Maryland College where he received his A.B. degree in 1936. He then entered the Johns Hopkins University School of Hygiene and Public Health as a graduate student in the Department of Biology under Professor Raymond Pearl. As a student and for some years thereafter, he conducted experiments in nutrition and population density effects on *Tribolium confusum* (the "confused flour beetle", as he called it).

From 1939 to 1941 he was an instructor in biology at the Johns Hopkins University School of Hygiene and Public Health. In 1941 he served as a consultant in child hygiene in the United States Public Health Service. The following year he joined the Office of the Air Surgeon, United States Air Forces, in Washington, D. C., where he served as a medical statistician until 1946. In that position he made analyses of injuries sustained in aircraft accidents and later assisted in the statistical analysis of the medical records on the Japanese victims of atomic bombing at Hiroshima and Nagasaki.

In September 1946, Dr. Schneider became Assistant Director of the Statistical Research Section of the American Cancer Society, a position he held until his death from a heart attack on September 22, 1960. He gained a high reputation for his work in the development of cancer registries. His position with the Society took him into 42 of the 50 states where he made literally hundreds of friends and admirers. Perhaps his strongest characteristic was his warm personality which endeared him to everyone.

Because of his heart condition, Aubrey was always well aware that his days were numbered, but he refused to allow it to bother him. Let him, in his own words, tell you his philosophy as expressed in a comment which he prepared for the March-April 1959 issue of *CA*.

"At the risk of facing all the hazards inherent in passing from the scientific to the philosophical, the writer would like to extend a word of encouragement to the physician because he, the writer, is also 'uninsurable'. At least he has never felt it advisable to pay the extra premium (quoted some years ago at a figure equivalent to the standard premium of a person twice his age at that time) just for the sake of having life insurance. The solution of the problem in his case required three things: (1) accepting the facts; (2) making a decision, and (3) living with that decision—peaceably. Strangely enough, the 'diagnosis' of uninsurability has not proven to be entirely 'fatal' over nearly half a century! As a matter of fact, it has had its compensations—largely in terms of the development of a philosophy of life which includes: (1) a deep sense of appreciation of being alive (in spite of physical limitations and nagging symptoms), and (2) a sound conviction that security can rest on something more substantial than a life insurance policy. This philosophy is probably better expressed by Bauer in the preface of his book YOUR HEALTH TODAY: 'The indomitable spirit with a broken spine is a better man than the Adonis with a wishbone where his backbone ought to be.' From such philosophy can spring an inner strength that is more valuable than the highest-priced life insurance policy ever written."

—E. CUYLER HAMMOND, Sc.D.

[Dr. Schneider's manuscript on the hospital cancer registry program which is published on pp. 173-174 of this issue of CA *was completed shortly before his death.*—ED.]

The Management of Head and Neck Cancer

Arthur G. James, M.D.

A large number of structures are packed within a limited space in the head and neck area. Malignant tumors may originate from any of these tissues. Because of the number of structures involved and their nearness to one another, the problems of diagnosis and therapy are complicated. The embryology of this area must be known in order to understand the presence of some of the lesions that occur. The management of malignant lesions in this area probably calls upon more clinical specialists than any other area of the body.

During the past few years, greater emphasis has been placed on the management of malignant lesions of the head and neck area, and increasing recommendations are being made for training physicians to treat these lesions. One of the prime functions of the Head and Neck Society, which was organized about five years ago, is to improve the treatment and end results of head and neck cancer.

Cancer of the head and neck is a readily accessible disease. In a recent study by Kinsey *et al.*, it was found that in a series of 150 cases of cancer of the head and neck area almost three fourths of the cancers could be directly visualized in the oral cavity. An additional 11 per cent could be palpated in the neck, and in only 10 per cent was a mirror examination necessary to locate the primary tumor. In a very small percentage of these cases the primary tumor was undetermined. These authors also reported that the five-year cure rate in a group of 150 cases with metastatic carcinoma of the neck was 33 per cent. This is certainly better than the prognosis of cancer in inaccessible regions such as the lungs, kidneys and parts of the gastrointestinal tract. On the other hand, since it should be possible to detect these lesions in their very early stages, it is surprising that the cure rate is not higher.

It has been reported by MacDonald that approximately 15 per cent of all cancer deaths, exclusive of deaths from brain tumors and malignant lymphomas beginning in the head and neck area, are due to primary head and neck cancer. The frequency with which the disease occurs should make it possible to improve the cure rate by early diagnosis and prompt and adequate treatment. It is important, therefore, that more information be disseminated concerning the detection and management of these lesions.

Detection

A careful history should first be taken. The physical examination should include inspection, palpation and auscultation. A biopsy should be done to confirm histologically any suspected lesion.

History

A careful history may prove to be very important. Benign lesions of the head and neck region are usually of long duration and are painless. Malignant lesions are of much shorter duration and are also painless. Inflammatory lesions, although they are of short duration, are painful. Congenital lesions are most apt to provide a history dating back to birth or soon thereafter. In the differential diagnosis of branchiogenic cyst and malignant tumor, the fact that a mass has been present for many years is significant. A history of recurrent enlargements of the parotid gland over a period of years may provide important information for the differential diagnosis of parotitis and carcinoma when that gland presents a firm, irregular mass.

Physical Examination

The examiner must have proper illumination, finger cot or rubber glove and a tongue depressor to carry out an adequate

From the Department of Surgery and Oncology, Ohio State University Medical Center, Columbus, Ohio.

Fig. 1. Palpation of base of tongue.

Fig. 2. Bidigital palpation of floor of mouth.

Fig. 3. Inspection of the mouth and pharynx.

examination. Although inspection is very important, palpation of the area may yield much more information (Figs. 1 and 2). The examiner should develop a definite routine in performing the examination.

INSPECTION—Discoloration, asymmetry, presence of a mass, ulceration, and changes in function are signs for which the examiner looks. Examination of the oropharyngeal cavity is too often carried out inadequately. The time-honored custom of simply depressing the tongue with a tongue blade and having the patient say "ah" gives only a superficial inspection of the tongue, cheek and the posterior pharyngeal wall (Fig. 3). Any number of early carcinomas in various parts of the oropharyngeal cavity could escape notice by this method. The examiner should use a headlight in order that both hands may be free for the examination. With a tongue blade it is possible to retract the lips away from the gums, the cheeks from the gingivobuccal gutters and the tongue from the floor of the mouth, so that all parts of the oral cavity are visualized. Adequate inspection of the tonsillar pillars, tonsillar fossae, posterior pharyngeal wall and soft palate should be performed while the tongue is depressed. Inspection of the oropharynx and nasopharynx requires the use of a laryngeal mirror. In most patients this maneuver can be done without anesthetizing the mucosal surfaces. However, in the occasional patient topical anesthesia may be needed to prevent gagging. Holding the patient's tongue with the left hand and the laryngeal mirror with the right hand, the examiner inspects the posterior surfaces of the tonsillar pillars, the vallecula, base of the tongue, pharyngeal wall and the larynx (Figs. 4 and 5). Then, by depressing the tongue with a tongue blade and reversing the mirror, he visualizes the nasopharynx (Fig. 6).

Most of the malignant lesions of the oropharyngeal mucosa are of the squamous cell type. The most common lesion is a simple ulcer. Occasionally a malignant tumor is seen originating in the minor salivary gland tissue. The base may be granular in appearance or may be covered with a grayish slough. If the lesion has

originated in a minor salivary gland, it is easily located submucosally as a tumor mass.

PALPATION—Palpation is a significant part of the examination. By palpation it is possible to determine whether a mound on the lip is an indurated or a firm lesion, enabling the differentiation of a malignant tumor from a submucosal retention cyst. In this way it is also possible to learn whether an area of leukoplakia has firmness and induration which may indicate the beginning of a malignant process.

The most important role of palpation within the oral cavity is in the examination of the base of the tongue (Fig. 1). Inspection of this area may indicate some asymmetry which may be due to a normal variation in the amount of lymphoid tissue on either side of the cavity. Palpation of the area should definitely reveal whether there is induration sufficient to raise the suspicion of malignancy. In cases where the epiglottis lies so close to the base of the tongue that the vallecula is not visualized on examination, it is possible to displace the epiglottis with the finger and by palpation determine that no malignant process exists.

In examining the neck for malignant lesions, palpation is probably the most important procedure. If the mass is located in the submaxillary area, it is well that a gloved finger be used within the mouth to press structures against the examining hand held underneath the chin (Fig. 2). In this maneuver the examiner should sit in front of the patient. The examination should proceed in orderly sequence with an evaluation of the submaxillary region, the jugular area (Fig. 7), and then the supraclavicular area. Mid-line structures should next be palpated, and then the region of the thyroid gland.

ROENTGEN EXAMINATION

X rays are invaluable in establishing the diagnosis of a bony enlargement. At times they will be useful in differentiating osteomyelitis from a primary bone tumor. We rely upon X-ray findings in making at least a tentative diagnosis of carcinoma of the paranasal sinuses. The use of a contrast

Fig. 4. Mirror examination of base of tongue.

Fig. 5. Indirect laryngoscopy.

Fig. 6. Mirror inspection of nasopharynx.

medium in one of the salivary glands in the performance of a sialogram may aid in establishing a diagnosis of tumor in that organ. Fluoroscopic observations of swallowed barium can yield valuable information about the pharynx and upper esophagus. The swallowing of air following deep inspiration will outline the trachea and larynx and often be of help in detecting abnormalities. A chest roentgenogram should certainly be a part of any examination for detecting malignant tumors of the head and neck area in order to rule out possible pulmonary metastases.

Biopsy

Final diagnosis as to the benignity or malignancy of a lesion is made by the pathologist. Since most lesions of the oropharyngeal cavity are readily accessible, the performance of a biopsy is a rather simple procedure. It may be done with either a small scalpel blade (Fig. 8) or a biopsy forceps. The specimen is excised from the margin of malignant tissue and should include surrounding normal tissue. Such a specimen provides the pathologist with sufficient material to determine whether there is infiltration of malignant cells into normal tissue.

In carrying out the biopsy, the operative field is prepared with a mild antiseptic solution and the area is anesthetized with a small amount of local agent before surgery. In most cases it is possible to control bleeding after surgery by applying pressure with a cotton pledget. Occasionally it is necessary to cauterize the base of the wound with a silver nitrate stick. Very rarely need the surgeon employ a needle and suture material to control bleeding. If the primary lesion is small, it may be judicious to perform an excisional biopsy, that is, one which removes the lesion *in toto*. There are several factors, however, that help to determine whether this should be done. If malignancy of the lesion is highly suspected, it is well to proceed with this method, especially when dealing with basal cell carcinoma. On the other hand, if there is much doubt about the diagnosis and if there would be a resulting deformity, it is better to perform a small biopsy and reserve the definitive excision for a later date. In dealing with moles which are suspiciously malignant, it is well to perform an excisional biopsy. If a mole proves to be malignant, the patient should be subjected to definitive surgery, either at a later date or, if the diagnosis can be established by frozen section, at the time of biopsy.

Biopsy procedures about the neck deserve special note with regard to technique. Two methods of biopsy are available, each of which offers certain advantages and disadvantages. The open or formal biopsy requires that an incision be made over the cervical mass, exposing it and removing either all or a portion of it for pathological studies. The pathologist will then have the advantage of a block of tissue for gross examination and eventual microscopic section. He will be able to learn more about this particular lesion than he would if he had only a few cells to observe. A formal biopsy of a mass in the neck should always be performed where surgical facilities permit more extensive surgery, should anything unusual develop. A node is often more deeply located than it seems to be, and its removal may be complicated by severe hemorrhage. Adequate exposure also is necessary in order to avoid damage to nearby structures. The sequelae of an open biopsy, however, are scarring and anatomical distortion in the area. Since most of the important cervical nodes are located between the jugular vein and carotid artery, this plane of tissue is usually obliterated in biopsying for metastatic carcinoma of the head and neck. If a radical neck dissection is to be employed later, this adds greatly to the difficulty of that procedure.

An aspiration biopsy creates no technical problem for subsequent surgery or X-ray therapy. In most cases, if we are dealing with metastatic carcinoma of the neck, it is not difficult to obtain enough tissue to make not only a smear but also a cell block of tissue. With this material the pathologist can learn just as much as if he had been given a formal biopsy specimen. In some cases where adequate tissue cannot be removed and it is not possible

Fig. 7. Bidigital examination of the thyroid.

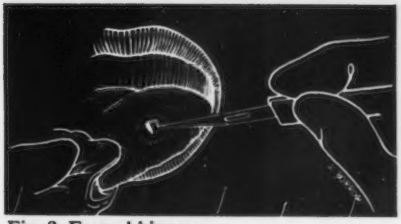

Fig. 8. Formal biopsy.

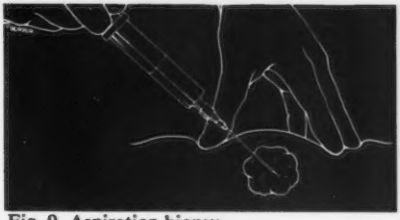

Fig. 9. Aspiration biopsy.

for the pathologist to make a diagnosis on the basis of a smear alone, a formal biopsy should be elected. If a node is involved by a primary lymphoma, it is often difficult for the pathologist to be certain of the diagnosis on the strength of aspiration biopsy material alone, and in such cases a node usually must be excised.

An aspiration biopsy is a very simple procedure (Fig. 9). It can be done readily in the office while the patient is being seen in follow-up. When such a biopsy is positive, it offers as much information as the more complicated formal biopsy. This procedure is usually performed in the following manner. The skin overlying the node is prepared with an antiseptic solution and anesthetized with a small amount of local anesthetic. The skin is then nicked with a sharp blade (in order to avoid the inclusion of superficial epithelium in the needle) and a 16 gauge needle with stylet in place is then inserted through the small nick and into the tumor mass. The stylet is included in order to prevent extraneous tissue from entering the needle tract. A 30 or 50 cc syringe is then attached to the needle and suction is applied by withdrawing the plunger. By applying mild rotary and to-and-fro motions, it is usually possible to obtain tissue from the tumor mass. Theoretically, an aspiration biopsy violates the same barriers as does the incisional biopsy. Although clinical material does not bear out the seeding effect of an aspiration biopsy, it has been shown experimentally that this may occur in mice in a significant percentage of cases.[1] However, since there is some danger of dissemination of cancer by using either method, and since there are some definite advantages to aspiration biopsy, this method should be employed often, especially in the diagnosis of metastatic carcinoma of the neck.

Treatment

Surgery was the first effective method of treatment for cancer of the head and neck area and many descriptions of radical surgery can be found in the older textbooks. Some of these procedures were abandoned years ago because of the risk of sepsis, but with the advent of the antibiotics many of them have again been found to be practical and effective. When radiotherapy became popular in the early decades of this century, most of these lesions were treated by radiation. However, after the initial enthusiasm for that method, it was found that there was a morbidity associated with adequate radiation and that many tumors were not controlled. Recent refinements in radiotherapy and the development of radioactive isotopes have increased the usefulness of this type of treatment for head and neck cancer.

The choice of treatment, whether radiation or surgery, depends upon the location of the tumor, histologic type, previous

treatment and whether the lesion is primary or metastatic.

Accessibility is necessary for adequate removal of the tumor by surgery. Complete resection is more feasible if a tumor is located in the anterior or middle portion of the oral cavity than in the posterior region or in the pharynx. Many such posteriorly located tumors are anaplastic and respond favorably to radiation therapy. If the involved tissue is close to bone, however, the bone will receive much of the radiation and therefore surgical resection is the preferred treatment in such cases.

The most common histological type of cancer occurring in the oral cavity is squamous cell carcinoma. Adenocarcinomas of the salivary gland and malignant melanomas occasionally appear. Radiation can completely control squamous cell carcinoma in many instances. Salivary gland adenocarcinomas and malignant melanomas are comparatively radioresistant and should be treated by wide surgical resection.

The method of treatment to be employed definitely depends upon the previous treatment of the lesion. If a cancerous growth which has been irradiated with intent to cure has persisted or recurred, radiation should not be used again unless only palliation is desired. Radiation effect on tissues is permanent. If, however, a lesion previously excised has recurred, the choice between further surgery or radiation is still open.

Most authorities agree that the treatment of choice for metastatic lesions in the neck is radical neck dissection. Radiation is used when necessary as a supplement to surgery.

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Cancer Training Program

The Bowman Gray School of Medicine announces a new training program in Radiation Biology and Cancer-Related Research. One-, two-, and three-year traineeships are being offered to research-oriented persons in the basic and clinical sciences. The traineeships are available at both the predoctoral and postdoctoral levels.

The program presents excellent opportunity for young research workers to learn radiation methodology and tracer techniques. First year trainees will be given a detailed survey of radiation biology as it relates to cancer research and will learn the techniques used in laboratory investigation. Second and third year trainees will have the opportunity to do independent research employing radiation methods in a chosen field of interest.

Applications are being accepted now for the course beginning in January 1961, and will be accepted until April 15, 1961 for the course beginning in July 1961. All inquiries should be directed to Dr. Donald J. Pizzarello, Executive Director, Radiation Biology and Cancer-Related Research Training Program, Bowman Gray School of Medicine, Winston-Salem, North Carolina.

Exfoliative Cytology of Pleural, Peritoneal and Pericardial Fluids

James W. Reagan, M.D.

History

In 1867, Lücke and Klebs observed lymphocytes and other larger round cells with large clear nuclei in a milky ascitic fluid said to be rich in cells. While this may be one of the earliest references to cancer cells in a body fluid, it is difficult to verify the cancerous nature of the cells on the basis of this brief description. The first authenticated description of cancer cells in pleural and peritoneal fluids appeared in 1882. In that year Quincke published a detailed description of cancer cells originating in ovarian and pulmonary cancer. Using cell films prepared from the sediment that formed when the fluids were allowed to stand, Quincke described the size, shape and arrangement of cancer cells in abdominal and pleural fluids. His observations were based on unstained preparations; however, iodine staining was employed in an attempt to distinguish between endothelial (mesothelial) cells and cancer cells.

In a discussion of his findings, Quincke referred to a case in which the presence of gastric cancer was first suspected on the basis of cancer cells found in pleural fluid. He emphasized that in the past too little attention had been given to the cells in body fluids and suggested that a study of the cells might give information of diagnostic value, not only in fluids related to cancer but also in effusions of inflammatory origin. In 1882, Ehrlich introduced new methods of fixation and staining which were adapted to a study of cellular preparations. Reference is made by him to three cases in which cellular studies of ascitic fluid were said to have first suggested a diagnosis of carcinomatosis. In 1895, Rieder identified dividing cells in the peritoneal fluid of a woman with "sarcoma carcinomatosum". Like Quincke, Rieder was aware of the difficulty in distinguishing cancer cells from mesothelial cells and cautioned that the polymorphism of mesothelial cells might be very misleading to the unwary microscopist.

While previous workers used direct cell films to examine the cellular content of the various body fluids, Bahrenberg, in 1896, described a new approach in which the fluid was clotted and the clot embedded in celloidin and then sectioned with the microtome. With this technique he successfully demonstrated cancer cells in the ascitic fluids from two patients with proved cancer. In 1897, Dock for the first time described the appearance of cancer cells derived from gastric and mammary cancer, and Warthin reported finding spindle-shaped cells in the pleural fluid from a patient with hemangiosarcoma involving the pleura. In 1899, Beneke described cells in ascitic fluid which were presumably from malignant melanoma, and in a pleural fluid noted cells which arose from a squamous cell carcinoma of the esophagus. In 1900, Mandlebaum described a technique for studying exudate. Using formalin fixation, celloidin embedding and sectioning, he was able to demonstrate *Actinomyces*, and later, in 1917, applied a similar approach to the study of tumor cells in exudates.

In 1901, Josefson introduced a new method for processing fluids which was similar to that used by Bahrenberg, except that preliminary centrifugation was used to concentrate the material. In 1911, Warren reviewed the literature and added several cases in which cancer was first sus-

From the Institute of Pathology, Western Reserve University and University Hospitals, Cleveland, Ohio.

pected on the basis of cellular studies of fluids. Quensel published a detailed work on cells in transudates and exudates in 1928. In this study, measurements of cells, nuclei and nucleoli were recorded in an attempt to distinguish between endothelial (mesothelial) cells and cancer cells. Despite the previous publications, Panton, in 1922, indicated that the feat of recognizing cancer cells was frequently asked of the pathologist but only rarely performed. He believed that the cytologic method was unsuitable because cancer cells only rarely became detached in any number so as to float freely in the fluid. In contrast, today it is known that cancer cells not only remain viable but also are capable of proliferating in fluid media. In many institutions all specimens of pleural, peritoneal or pericardial fluid are now being subjected to a detailed examination of their cellular content.

Methods of Processing

The early workers used direct cell films to study the cells in fluids, and many pathologists still utilize this method. The advantages are said to be better nuclear staining, less cell shrinkage and possibly greater accuracy when dealing with small amounts of fluid.[38] With this approach, centrifugation or some other means must be provided to concentrate the cells. Preliminary defibrination[41] may produce a better yield of cells, and acetic acid may be added to bloody fluids to lyse the erythrocytes.[38] Fawcett has described a method whereby bloody fluids can be effectively concentrated and the cancer cells segregated by differential centrifugation.

A relatively simple method of processing fluids for study by direct cell films has been described by Papanicolaou. An aliquot of unclotted fluid is mixed with an equal part of 50% alcohol, centrifuged for 30 minutes at 2,500 rpm, and the supernatant fluid is decanted. Several drops of Mayer's albumin are mixed with the sediment. The sediment is removed from the centrifuge tube with a small curette and spread over the surfaces of several glass slides. The cell films should be allowed to dry at the edges prior to fixation in ether-alcohol solution. The cells will be kept in place during staining by coating the slides with a thin layer of celloidin.

Another approach uses the so-called cell block technique. This may be used alone or in combination with the direct cell film method. With the cell block technique there is a greater concentration of cells per unit of area on the slides and the majority of cells are in the same focal plane.[38] In addition, cell arrangement can be studied more effectively and special stains can be utilized to gain more information about the cells identified or to search for acid-fast organisms. A great variety of fixatives can be used, including formalin,[1,11,16,22,28] picric acid,[5,20] Zenker's solution,[7] Orth's solution[40] and alcohol.[2] The material is concentrated by centrifugation and various procedures are used to hold the cell mass together for processing. This can be accomplished by the fixative itself[2,24,25] or by the use of thrombin.[4,6,15] Gelatin[26] and a sausage skin[46] also have been used. Another technique utilizes freezing for this purpose.[42]

The following procedure has proved to be satisfactory for preparing fluid samples for cell block studies. An aliquot of unclotted fluid is centrifuged for 15 minutes at 2,500 rpm. The supernatant fluid is decanted and the sediment is covered with 10% formalin and placed in a warm water bath for 10 minutes. At the end of this time the packed sediment is usually floating. If not, it is carefully dislodged by means of an applicator stick. The cell mass can then be processed in the same manner as a tissue specimen. Several sections should be prepared to obtain the greatest accuracy.

Purpose

Cytologic studies of pleural, peritoneal and pericardial fluids are done to gain knowledge of the etiology of the transudate or exudate. Although unsuspected cancer may be discovered by this method, seldom will the lesion be an early cancer. The study should not only entail a search for cancer cells but also provide informa-

tion about the other cellular components in an attempt to learn the etiology of the effusion.

Non-neoplastic Effusion

The pleural, peritoneal and pericardial cavities are lined by a single layer of flat polygonal epithelial cells, referred to as the mesothelium. Under normal conditions there is little or no fluid in the cavities; however, under pathologic conditions exudate or transudate may collect in large amounts. These fluids may contain mesothelial cells, histiocytes, leukocytes, erythrocytes and, rarely, cells which are introduced in the process of collecting the fluid.

One of the most common cell types observed is the mesothelial cell. Although polygonal in form when *in situ*, it is more often round in the fluid medium since the external forces are acting equally on all parts of the cell. When the cell is isolated, the cytoplasm is relatively dense and may be acidophilic or basophilic. Cytoplasmic vacuolization may be present, as well as a dense ectoplasmic zone. The latter may be related to the brush border, although some investigators have attributed it to shrinkage. The nucleus is relatively large, with a delicate network of chromatin in which there are one or several small nucleoli. Usually there is a single nucleus, although binucleation is not rare and multinucleation may occur. Although they are usually isolated, mesothelial cells may occur in strips, sheets or aggregates as, for example, a pseudoglandular arrangement. Groups of cells are more often observed in the presence of a hypertrophic or proliferating mesothelium. Under these conditions, the nuclei, which are usually rather uniform in size and shape, may become larger and more variable in size. The chromatin becomes coarser and the nucleoli more prominent. Large vacuoles may exist and so-called signet-ring forms may result. Even phagocytosis of other cell types may occur. Such changes may be seen in patients with cirrhosis or congestive heart failure (Fig. 4).

Histiocytes are more variable in size than the mesothelial cells. Their cytoplasm is diffusely and finely vacuolated and has less affinity for the cytoplasmic dyes. The cytoplasmic boundary is ill-defined and the cells may have one or more nuclei. They are infrequent in some transudates but are common in exudates related to resolving infection.

The leukocytes include neutrophiles, eosinophiles, smaller mononuclear cells and lymphocytes. The first are common in the suppurative processes. Lymphocytes are abundant in effusions related to congestive failure and tuberculosis. In the latter, the mononuclear cells may be so numerous and immature as to suggest cells from lymphosarcoma.

Although more commonly seen in the presence of neoplastic effusions, erythrocytes may be observed in inflammation or other destructive processes. Trauma associated with paracentesis or thoracentesis may also account for the erythyrocytes.

Rarely, squamous cells may be introduced by the trocar in obtaining the fluid specimens. Under these conditions, the cells occur only in sheets and not as isolated cells. They can therefore be distinguished from cells originating in squamous cell cancer.

Neoplastic Effusion

The malignant tumor cells observed in pleural, peritoneal and pericardial fluids are variable in their appearance. Their features are in part related to the type of neoplasm which exists. Approximately 60 per cent of the neoplasms related to effusions are classified as adenocarcinoma; 30 per cent represent other forms of cancer, and only about 10 per cent are sarcomas or other types of malignant tumors.

The cells originating in either adenocarcinoma or other forms of cancer are variable in size and shape. Their cytoplasm is usually poorly defined and stains basophilic or indeterminate, and less often acidophilic. Vacuolization is a prominent feature of some cells derived from adenocarcinoma, and the nucleus may be displaced by the accumulated secretion. Unless compressed, the nucleus is usually large in relation to the cytosome and may

Table 1

Correlation of Fluid Studies Prior to Death
and Autopsy Findings in 369 Patients with Effusions

AUTOPSY FINDINGS	NO. PATIENTS	CYTOLOGIC INTERPRETATION OF FLUID SAMPLES PRIOR TO DEATH	
		No. patients malignant cells found	No. patients malignant cells not found
Effusions with malignant tumor	207	153 (73.9%)	54 (26.1%)
Effusions without malignant tumor	162	1 (0.7%)	161 (99.3%)
TOTAL	369	154	215

be variable in size and shape. Multinucleation is common and the nuclear chromatin may be coarsely granular, hyperchromatic and arranged in larger chromocenters. One or several large nucleoli may be observed and these may be of a bizarre configuration. They are more common in the cells of adenocarcinoma (Fig. 1). In some cases, both normal and abnormal mitoses are abundant, although this is not a constant finding. The cells may be isolated or arranged in some type of grouping. Proliferation spheres are common in mammary cancer (Figs. 2 and 3), while acinar arrangements and papilliferous structures are more numerous in ovarian cancer. Other organoid arrangements may be observed, depending on the type of cancer. Degenerative changes are prominent in many forms of cancer. A focal deposition of calcium is not uncommon in ovarian, mammary and pancreatic cancer. The cells originating in sarcoma are, in general, more uniform in size and smaller than cancer cells. They are more often isolated and have a relatively large nucleus surrounded by a limited amount of cytoplasm. In contrast to the nuclei in cells from cancer, the nuclei in cells from sarcoma are more uniformly altered (Fig. 5).

Results

With few exceptions, the earlier workers were concerned only with a description of the cells observed in one or several body fluids from patients with cancer, and it was not until 1924 that Seecof and Boetsch evaluated this approach. These authors concluded that there was agreement between the cellular evidence and the autopsy findings in 75 per cent of the specimens of pleural fluid and in 78 per cent of the peritoneal fluids. Over the next three decades, there were many reports evaluating the accuracy of the approach.[1,7,8,11,14,16,19,22,24,25,29,32,37-39,47] In most of these studies there was an accuracy of 50 to 80 per cent, while in 3 to 10 per cent of the specimens the cellular evidence of cancer was not confirmed.

To determine the accuracy of this approach in our own institution, all autopsies of patients having fluid studies prior to death were reviewed in order to correlate the cellular and histopathological findings. Over a period of some 28 years, 673 fluid samples have been studied in 369 patients who were ultimately autopsied. As shown in Table 1, there were 207 patients who had malignant tumor and effusion in one or more of the body cavities. Of these, 153 (73.9%) had demonstrable tumor cells in one or more fluid samples examined prior to death. This value is comparable to the previous accuracy of 74.3 per cent published earlier.[25] Represented among the autopsied cases was only one in which a cellular interpretation of cancer was not verified at autopsy, representing an error of 0.7 per cent. Of 162 patients who did not have malignant tumor at necropsy, 161 had no evidence of malignant tumor in the fluid samples studied.

Table 2

Results of Fluid Studies in 207 Autopsied Patients with Effusion and Malignant Neoplasm

SITE OR TYPE OF PRIMARY NEOPLASM	NO. CASES	NO. CASES MALIGNANT CELLS FOUND	PER CENT ACCURACY
Pulmonary tract	55	42	76.4
Ovary	29	27	93.1
Breast	28	24	85.7
Lymphoma-Leukemia	25	15	60.0
Gastrointestinal tract	17	12	70.6
Liver-gall bladder	12	7	58.3
Pancreas	11	7	63.6
Uterus	8	8	100.0
Urinary tract	7	2	28.6
Soft tissues	3	2	...
Pharynx	2	1	...
Thyroid	2	1	...
Prostate	2	1	...
Adrenal	2	1	...
Unspecified	4	3	...
TOTAL	207	153	73.9

On the basis of this study done in skilled hands, it is evident that the identification of malignant tumor cells carries a high validity. However, 25.1 per cent of the samples which were reported as not containing malignant tumor cells proved to be from patients with effusions related to malignant neoplasms. A negative report, therefore, does not exclude the presence of malignant neoplasm. There are many possible explanations for this discrepancy. As shown in Table 2, the ability to demonstrate malignant tumor cells is related to the type of tumor. The types of cancer which are more commonly associated with effusion, *i.e.*, cancer of the lung, breast, ovary and gastrointestinal tract, are more readily recognized, while others are more difficult to detect. Only 73.9 per cent of the neoplasms were identified in the fluid samples submitted. It should be emphasized that not all of the neoplasms were situated in locations that would have allowed the cells to be readily shed into the fluid studied; only about 80 per cent of the neoplasms were of such size and so situated anatomically. Of some interest is the rather high accuracy for demonstrating ovarian cancer not only in ascitic fluid but also in pleural fluid. Many of these patients were not recognized as having ovarian cancer until the fluid findings were reported.

Of the samples represented, 69 per cent consisted of pleural fluid, 30 per cent were ascitic fluid and 1 per cent were fluids from the pericardial space or other sites. A similar predominance of pleural fluids is found in most studies. Of those patients who had intrathoracic neoplasms associated with fluid accumulation at autopsy, 83.3 per cent were identified in pleural fluid studies. Cells were demonstrable in the ascitic fluids from 73.7 per cent of the patients with intra-abdominal neoplasms. In only two of four patients having a malignant tumor involving the pericardium were malignant cells detected in the pericardial fluid.

At present, the cytological approach to body fluids is of value not only in demonstrating the presence of unsuspected cancer, but also in gaining information about the origin of the transudate or exudate which is present. Only in the last decade have attempts been made to determine the

primary site by studying the cells of a fluid sample. The site of origin of the malignant neoplasm can be predicted accurately in only about 50 per cent of the cases, even in experienced hands. It is possible that with the use of cytochemistry the method may be of greater accuracy at some future time.

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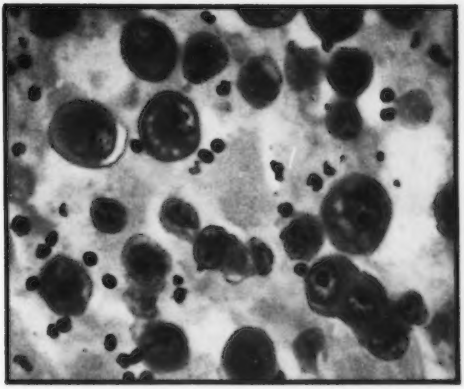

Fig. 1. Malignant tumor cells in pleural fluid from patient with primary adenocarcinoma of lung. Cell block technique. (×500)

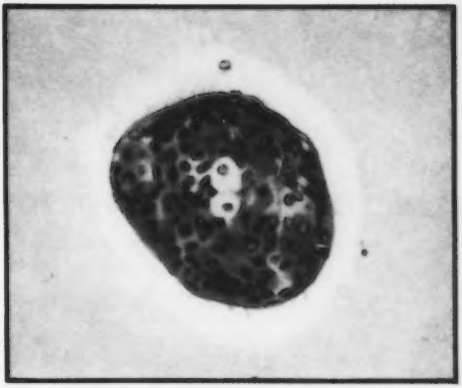

Fig. 2. Malignant cells in pleural fluid of patient with widespread mammary adenocarcinoma. Cell block technique. (×440)

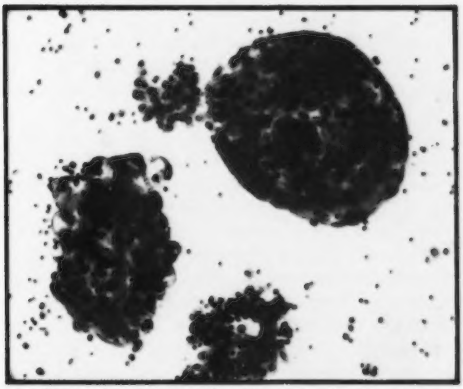

Fig. 3. Aggregates of malignant cells in ascitic fluid from patient with widespread carcinomatosis. Direct cell film technique. (×340)

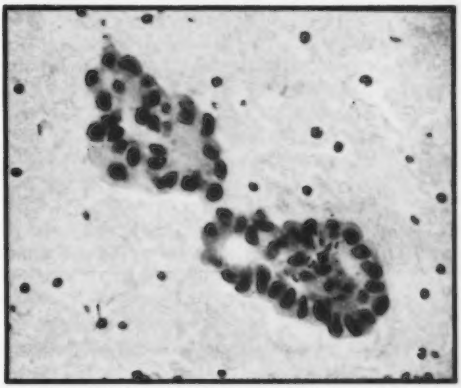

Fig. 4. Acinar-like groups simulating adenocarcinoma. Pleural fluid. Congestive heart failure. Cell block technique. (×440)

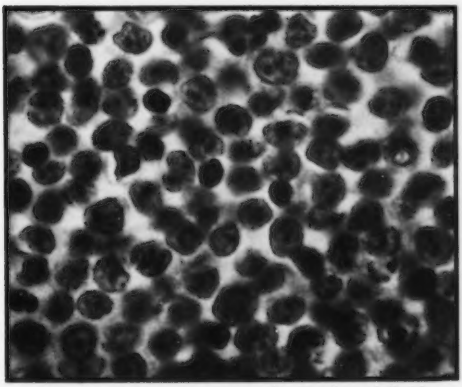

Fig. 5. Malignant tumor cells in pleural fluid from patient with malignant lymphoma. Cell block technique. (×500)

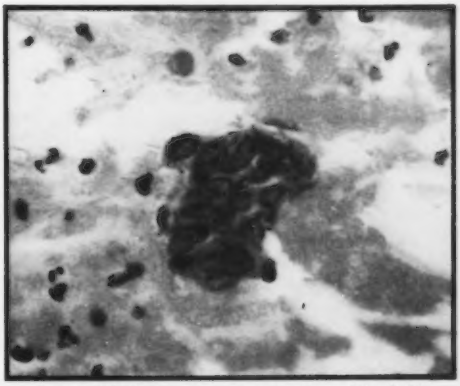

Fig. 6. Malignant tumor cells in ascitic fluid from patient with proven Wilms' tumor. Cell block technique. (×900)

Oral and Laryngeal Exfoliative Cytology

William O. Umiker, M.D.

Oral Cytology

Unlike many other applications of exfoliative cytology, oral cytology has received relatively little attention, probably because of the ease with which visual and histopathologic diagnosis of most neoplasms of the mouth is made. Nevertheless, the following diagnostic and prognostic information derived from cytology may complement that obtained by histopathologic study: (1) evaluation of premalignant lesions; (2) early detection of carcinoma; (3) routine diagnosis and grading of squamous cell carcinomas; (4) evaluation of radiosensitivity; (5) diagnosis of residual and recurrent cancer, and its differentiation from radionecrosis.

The successful treatment of oral cancer depends upon early suspicion, visualization and biopsy. The diagnosis should be established by biopsy whenever possible, but when multiple or large lesions create problems of selection of biopsy site or necessitate many biopsies, direct smears permit the screening of the entire abnormal surface. The most common premalignant lesion of the oral cavity is leukoplakia. Oral smears from areas of leukoplakia may reveal the degree of epithelial atypism and early malignant change.[7,10] Hopp, using data from his own series and the reports of several investigators, found that the diagnostic sensitivity of oral smears from 418 known cancers of the mouth was over 96 per cent.

Despite the high diagnostic accuracy of the cytologic method, oral smears should be used as an adjunct rather than as a substitute for biopsy since their combined use increases the over-all diagnostic sensitivity. Oral smears are especially useful when a biopsy fails to disclose a malignant neoplasm and the advisability of rebiopsy is equivocal because the index of suspicion is low. Likewise, an occasional unsuspected carcinoma will be revealed by taking smears from apparently innocent lesions of the mucous membrane. Using oral smears, Silverman and his associates discovered four unsuspected cancers in a group of 60 ulcers which did not appear to be neoplastic and would otherwise not have been subjected to biopsy.

The microscopic grading of squamous cell carcinomas should be accomplished primarily by histopathologic examination. However, when a biopsy specimen is too small or the microscopic details are clouded by secondary inflammation, necrosis or artifact, oral smears may be a valuable adjunct for the grading of the neoplasm.[9]

During X-ray therapy of oral cancer, oral smears provide a painless, atraumatic method for the study of irradiation changes in the tumor. A numerical increase in malignant cells in smears is found during the first week or two, probably reflecting greater exfoliation of the neoplasm at that time.[11] Preliminary observations suggest that patients whose smears consistently contain abundant malignant cells are more prone to develop lymph node metastases.[11,12] Malignant cells from radiosensitive cancer may disappear from oral smears within one or two weeks of external irradiation, while those from more resistant cancer persist throughout the course of treatment. The presence of malignant cells in smears taken at the completion of treatment does not necessarily indicate failure of radio-

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therapy since some of these patients may still go on to clinical cure. Unfortunately, negative smears during the later phases of X-ray treatment do not rule out the presence of residual neoplasm and are therefore of questionable practical value. However, when a tumor persists, malignant cells usually reappear in smears taken several weeks later. The optimal time for posttreatment smears has been found to be eight weeks after the start of treatment, residual neoplasm having been demonstrated in all patients who have positive smears at that time.[11]

At the completion of radiotherapy there may be a residual ulcer which represents either persistence of neoplasm or an area of radionecrosis. Radiotherapists are loath to biopsy such lesions during the immediate postirradiation period, as the biopsy site may serve as a "focus minoris resistentiae" and histopathologic interpretations are sometimes difficult. The presence of malignant cells in smears from such lesions may be a valuable aid in this important differential diagnosis.[1,8,11] Nevertheless, such smears should be interpreted with caution since benign irradiated epithelial cells may simulate malignant cells.

Monthly cytologic examinations during the postirradiation or postoperative observation period may provide the first evidence of recurrent neoplasm. Malignant cells have been observed in follow-up smears weeks before clinical or histopathologic evidence of carcinoma.[10] A few recurrent or residual cancers do not involve the surface mucosa, thus precluding the possibility of demonstrating cancer cells in oral smears.

It must be emphasized that smears taken during and following irradiation should be examined by a cytologist who has had considerable experience with such material, because the interpretative difficulties which are encountered in histopathologic preparations are reflected in cytologic preparations.

Method

Oral smears are obtained directly from the lesion by using a moistened tongue blade, a dull metallic blade or a curette. Montgomery[3] recommends the use of Woodson's No. 2 metal plastic instrument. Cotton-tipped applicators are not recommended because much of the material is absorbed in the cotton and thereby lost. The material is spread evenly on glass slides and fixed and stained by the standard Papanicolaou technique. There must be minimal delay in immersing the smears in fixative because they dry very rapidly.

Interpretation

NORMAL (Fig. 1)— Smears from normal oral mucous membranes present a clear, tidy appearance and consist almost exclusively of superficial squamous cells, cornified (yellow or pink) or noncornified (green). Smears from the cheek, soft palate and ventral surface of the tongue contain many noncornified cells, while those from other areas, particularly the gingiva and dorsal surface of the tongue, have more cornified cells.[2,3] Unlike smears of vaginal secretions, oral smears seldom include cells from the deeper layers of the mucosa. Although there is some similarity in the processes of maturation of oral and vaginal mucosae, any effect of sex and menstrual cycle on the cellular pattern of the former is doubtful.[5,15,16] There are variable numbers of bacteria, some of which may be within epithelial cells. Fungi are often seen, especially in smears from the gingiva or tonsil.

INFECTION—Numerous polymorphonuclear leukocytes and variable numbers of lymphocytes, plasma cells, histiocytes and erythrocytes are found in smears from infected areas. The squamous cells show more variation in size and shape, and distorted or degenerating cells are more common. Bacteria are abundant. The combination of exudate and bacteria and cellular detritus gives the smears a disorderly, untidy appearance.

LEUKOPLAKIA (Figs. 2, 3, 4)—The most constant change in smears obtained from areas of leukoplakia is an increase in the percentage of cornified cells, many of which exhibit perinuclear vacuolization.[4,7,15] Montgomery and von Haam[4] also noted increased keratinization of cells from normal areas in patients who had

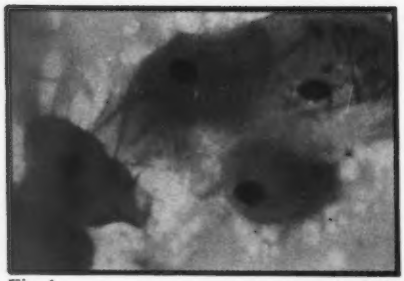


Fig. 1 (× 380)

Fig. 1. Negative oral smear. Benign superficial squamous cells.
Fig. 2. Oral leukoplakia. Keratinization and loss of nuclei. Note hyperchromatic nucleus.
Fig. 3. Oral leukoplakia. Squamous cells with atypical nuclei. Note bacteria in cells.
Fig. 4. Oral leukoplakia. Marked acidophilia of cytoplasm and atypism of nuclei.
Fig. 5. Oral squamous cell carcinoma. Note cornified cell, "tadpole" shape.
Fig. 6. Oral squamous cell carcinoma. Note cornified cell with increased chromatin.
Fig. 7. Oral squamous cell carcinoma. Note small cluster of squamous cells.

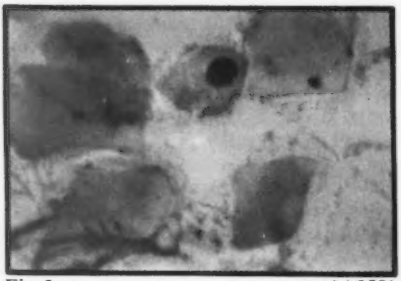
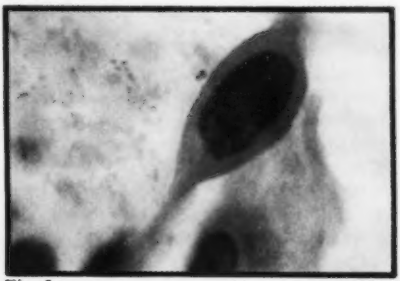


Fig. 2 (× 380)



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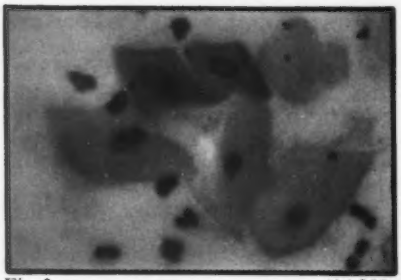

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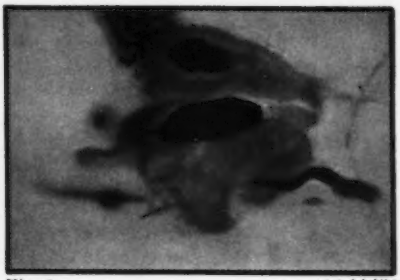

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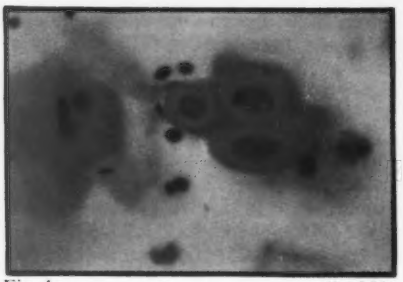


Fig. 4 (× 380)

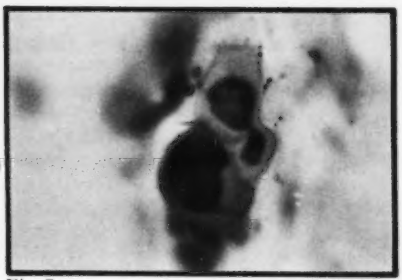


Fig. 7 (× 1140)

Fig. 8. Poorly differentiated oral carcinoma. Large cells, scanty cytoplasm, giant nuclei.
Fig. 9. Oral squamous cell carcinoma during irradiation. Large cell, clumped chromatin.
Fig. 10. Squamous cell carcinoma of larynx. Malignant "tadpole" squamous cell.
Fig. 11. Squamous cell carcinoma of larynx. Cell disproportion and clumped chromatin.
Fig. 12. Squamous cell carcinoma of larynx. Noncornified cell with basophilic cytoplasm.
Fig. 13. Squamous cell carcinoma of larynx after irradiation. Malignant features marked.
Fig. 14. Squamous cell carcinoma of larynx after irradiation. Bizarre nuclei; vacuolation.

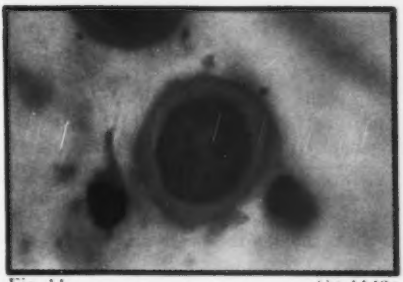


Fig. 11 (× 1140)

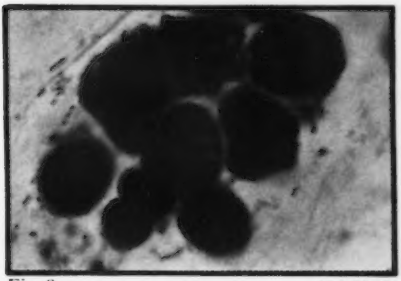
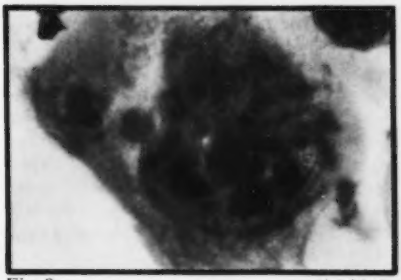


Fig. 8 (× 1140)

Fig. 12 (× 1140)



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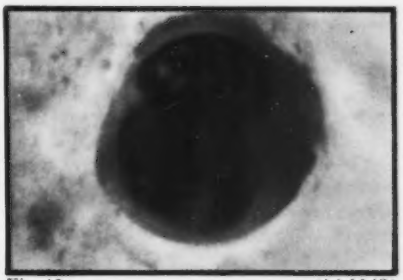


Fig. 13 (× 1140)

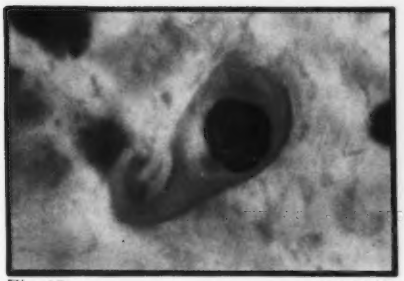


Fig. 10 (× 1140)

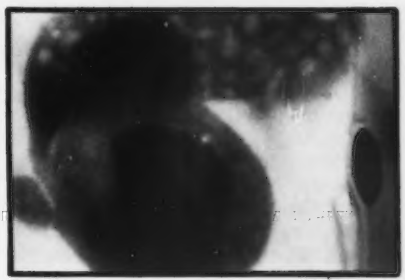


Fig. 14 (× 1140)

leukoplakia. The nuclei may show either no abnormalities or atypism, such as enlargement, hyperchromatism, clumped chromatin, thick nuclear borders and variations in size and shape.[7,10] The atypism is usually minimal but may be so severe that differentiation from carcinoma is difficult, although atypical benign cells tend to remain in sheets or large clusters, while malignant cells are more frequently solitary or in small groups.[7,10] When the abnormalities are marked, malignant transformation is likely.

CARCINOMA (Figs. 5, 6, 7, 8, 9)—The vast majority of oral cancers are epidermoid carcinomas, and the malignant squamous cells which are found in direct oral smears mimic those found in sputum or vaginal secretions. Irradiated malignant cells show enlargement, increased vacuolization, bizarre and multinucleated forms and alterations in staining reaction. In the early phases of treatment, the malignant features are accentuated; later, the changes are chiefly those of degeneration. Occasionally an increase in the percentage of mature malignant cells is observed. In addition to malignant cells, these smears show many more leukocytes, bacteria and debris.[13] The benign squamous cells often present an untidy, ragged appearance and sometimes may exhibit atypism similar to that seen in leukoplakia. Erythrocytes, macrophages, shreds of mucus and particles of retained food may also be present in the smears.

Laryngeal Cytology

Laryngeal cancer can be diagnosed cytologically by direct smears taken from a cocainized larynx during mirror laryngoscopy. A fine camel's-hair brush,[14] aspirating tip or cotton-tipped applicator may be used to obtain the secretions, but the cotton tips are least preferred. These techniques can be performed as office procedures. Satisfactory cytologic results can also be obtained by the examination of sputum, although fewer malignant cells are found in sputum than in direct smears.[10] At least three sputum specimens should be examined if the first smears are negative for malignant cells. It should be emphasized that cytologic examination should not replace the biopsy and is unnecessary for the diagnosis of most forms of laryngeal cancer. However, as in the case of oral smears, it may provide supplemental information, especially when the initial biopsy is equivocal or negative. The accuracy of laryngeal exfoliative cytology in the diagnosis of very early carcinomas or of premalignant lesions, such as leukoplakia, remains to be investigated.

Exfoliative cytology may be a useful adjunct in the follow-up of patients who have received operative or irradiation treatment for cancer of the larynx. Sputum specimens or direct smears examined at frequent intervals may reveal residual or recurrent neoplasm before clinical or histopathological evidence is manifest.[10] The number of malignant cells with their characteristic cytologic features may increase appreciably during the first two weeks of X-ray irradiation. During the later phases of the treatment, the smears are usually negative even when there is residual neoplasm. However, the smears of such patients frequently become positive a few weeks after treatment has been completed. Since most residual or recurrent carcinomas have surface involvement, false negative smears are not common.

Smears from laryngeal carcinomas contain cells which are similar to those from bronchogenic cancer, but they have a higher incidence of well differentiated cornified squamous cells (Figs. 10, 11, 12). Direct laryngeal smears show more superficial squamous cells, more ciliated columnar cells and fewer alveolar histiocytes than do smears of sputum.[14] It is recommended that postirradiation smears be interpreted only by cytologists who have had considerable experience with this type of material because the changes induced by irradiation may be confused with those of carcinoma (Figs. 13 and 14).

(See references on page 169.)

Exfoliative Cytology of Cerebrospinal Fluid

Lawrence J. McCormack, M.S., M.D., M.S. (Path.)

A search for tumor cells in the cerebrospinal fluid can aid greatly in the diagnosis of certain bizarre neurologic conditions.[1,3,4] The semicomatose patient with baffling neurologic findings, whose cerebrospinal fluid contains few cells yet has a low glucose content, may be spared many hours of diagnostic study by the procedure. It is not essential to use the method on fluids aspirated from operative neoplasms of the central nervous system because tissue is readily obtainable at the time of surgery; examination of a frozen section of tissue from the lesion is a more accurate method of assessment. Consequently, this study was limited to the examination of cerebrospinal fluid removed at lumbar puncture or occasionally obtained at the time of ventriculography.

Method of Wet-Film Technique[2]

Several problems are involved in the preparation of fixed films of cerebrospinal fluid. A major problem concerns fluid specimens with low cell counts; since there is a lack of adhesion between cellular elements and the slide, the few cells present may be lost. This difficulty was successfully overcome by employing a wet-film method that has been of equal advantage in the study of body fluids removed from other sites. The wet-film technique causes only minimal alteration of cytologic elements and precludes formation of fixation artifacts. Furthermore, since wet-film preparations are easy to make, the rapid study of several aliquots of the original fluid is possible and thus many more cells are available for interpretation.

From the Department of Anatomic Pathology, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Staining Fluid

The constituents of the staining fluid are: 1 gm of toluidine blue O (histologic); 20 ml of 95% ethyl alcohol; and 80 ml of distilled water. The dry stain is ground in a mortar with the alcohol, and the water is added slowly. The resulting solution is transferred to a glass-covered bottle. Ten ml of the toluidine blue solution is then added to 10 ml of horse serum,* and the mixture is centrifuged to remove any sediment. The supernate constitutes the staining fluid which is decanted. A few thymol crystals are added. The solution is then poured into a glass-stoppered bottle and is stored in the refrigerator. It remains stable for several months; the only drawback has been the occasional slow growth of fungi within it.

Preparation of Wet Films

The wet films are prepared in the following way. A specimen of cerebrospinal fluid (5 to 15 ml) is centrifuged at 2,000 rpm for 10 minutes. The supernate is decanted and discarded. A drop of staining fluid is placed on a clean glass slide and a drop of sediment from the bottom of the centrifuge tube is mixed with it. The drop of stain must not be so large that the final preparation is opaque. A coverglass is placed on the slide and the preparation is then studied under the microscope.

Fixed films, if desired, can be prepared at the same time and dropped into acetic acid-alcohol (97 ml of 95% alcohol; 3 ml of acetic acid). This fixative is employed instead of the usual alcohol-ether; it is equally satisfactory, more stable, less offensive and not nearly so flammable.

**Difco Bacto-Horse Serum, Difco Laboratories, Detroit.*

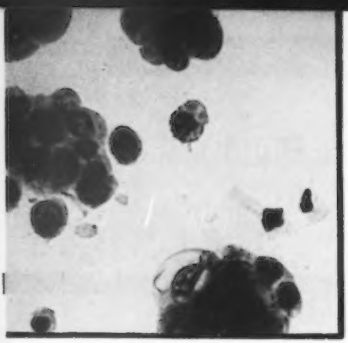


Fig. 1

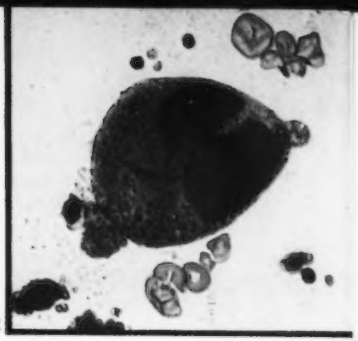
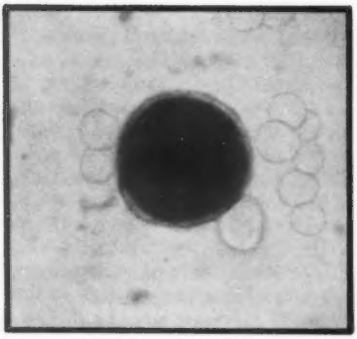


Fig. 2

Fig. 3



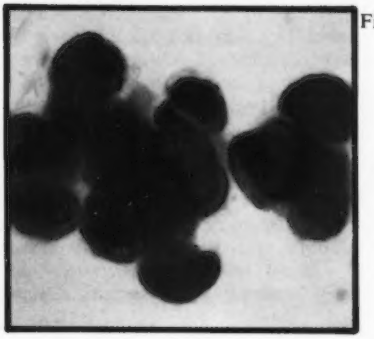


Fig. 4

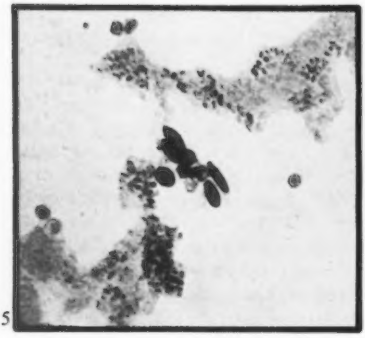


Fig. 5

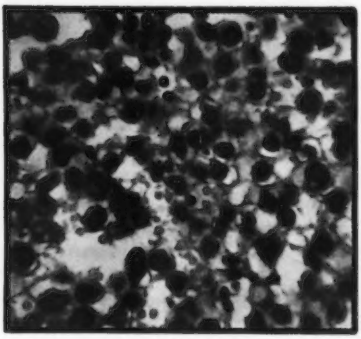


Fig. 6

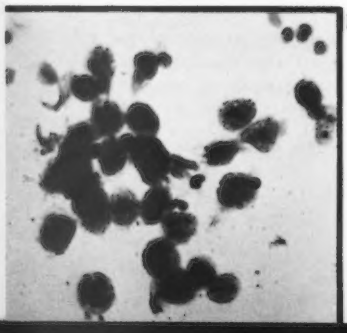
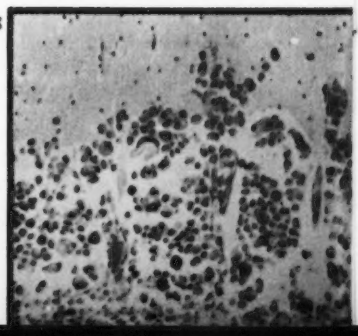


Fig. 7

Fig. 8



After study, wet-film mounts may also be permanently preserved: the slide and coverglass are separated and both are dropped into a bottle of the fixative; the horse serum in the stain is a good adhesive. Both the slide and the coverglass are stained by the Papanicolaou technique; they are remounted, and marked cells can be found again.

Cytologic Interpretation

The diagnosis of neoplastic cells in cerebrospinal fluid is based upon the same criteria that are used for other body areas (Figs. 1, 2, 3, 4). However, in examining the wet mounts certain cautions must be observed. Hyperchromatism is not often a prominent feature of the neoplastic nuclei; one is much more likely to see considerable detail in large and irregular nuclei. The size of nuclei and of all cells is approximately one-third larger in wet than in fixed films. As a consequence, simple histiocytes may closely simulate tumor cells. Also, two nonneoplastic cellular findings may simulate neoplastic elements: (1) the occurrence of oval and elongated nuclei that only rarely are surrounded by cytoplasm—these are the remnants of desquamated ependymal cells (Fig. 5), and (2) the occurrence of large macrophages that contain quantities of various debris, including leukocytes, nuclear particles and erythrocytes.

It must be remembered that the bizarre neurologic symptoms of the patients may be caused by certain fungous diseases. The disease most commonly observed is caused by *Cryptococcus neoformans*, a fungus that stains well and is easily identified in the wet-film preparation.

Findings

This discussion is based on the cytologic study of specimens of cerebrospinal fluid from 616 patients. In approximately 6 per cent of the patients more than one specimen was studied. A second specimen, and rarely a third, was obtained when any abnormality was detected. Occasionally, when the initial specimen showed only minimal abnormalities, a second specimen disclosed neoplastic cells. This delayed finding led to the speculation that the taking of the first sample may predispose the cerebrospinal fluid to alterations in dynamics which dislodge initially adherent neoplastic cells.

Tumor cells were unequivocally identified in specimens from 28 patients; in two others immature lymphoblastic forms were found. Experience has proved that it is not possible, from the study of the exfoliated cells, to make a differential diag-

Legends

Fig. 1. Cluster of cells exfoliated from metastatic carcinoma of lung. Cerebrospinal fluid. Toluidine blue O stain. (×450)

Fig. 2. Tumor giant cell from metastatic mammary carcinoma. Crystals are talc. Cerebrospinal fluid. Toluidine blue O stain. (×450)

Fig. 3. Mitosis in cell from metastatic melanoma. Cerebrospinal fluid. Toluidine blue O stain. (×750)

Fig. 4. Cluster of neoplastic cells in an indeterminate case. Cerebrospinal fluid. Toluidine blue O stain. (×900)

Fig. 5. Naked elongated nuclei commonly found and interpreted as ependymal in origin; not neoplastic. Cerebrospinal fluid. Toluidine blue O stain. (×450)

Fig. 6. Tissue section of pineal seminoma, removed surgically. Hematoxylin and eosin stain. (×450)

Fig. 7. Neoplastic cells from pineal seminoma (same case as Fig. 6) exfoliated approximately six months later. Subsequent irradiation eradicated the sources of the cells; normal findings five years later. Cerebrospinal fluid. Papanicolaou stain. (×450)

Fig. 8. Diffuse meningeal carcinomatosis of pancreatic origin. Note profuse number of cells in subarachnoid space and invading perivascular spaces. Hematoxylin and eosin stain. (×450)

nosis between primary and metastatic lesions of the central nervous system. Consequently, all of the available information must be utilized to determine the source of these tumor cells.

In 20 of the patients the responsible lesions were finally diagnosed as metastatic intracranial neoplasms. Nine of these patients had carcinomas that were previously recognized and treated. In seven other patients the source of the neoplasm was established only at necropsy. The sources of the primary neoplasms were: breast (six patients); lung (five patients); gastrointestinal tract (five patients) including stomach (two patients), pancreas (two patients), hepatic bile ducts (one patient); melanoma (two patients); antrum (one patient); and prostate (one patient). Other changes were found in the cerebrospinal fluid of these 20 patients. The cell counts varied widely, ranging from no cells to 4,500 per cubic millimeter, as enumerated in the counting chamber. More than half of the patients had less than 50 cells per cubic millimeter, on at least one cell count. Therefore, a low cell count does not guarantee the absence of neoplastic cells, but a low cell count in conjunction with a low content of sugar in the cerebrospinal fluid urges a search for abnormal cells. Some well-qualified observers can recognize in the routine counting chamber the large, irregular cells that are abnormal and require further study.

The sugar content of the cerebrospinal fluid at times was greatly altered in this group of patients, a finding that can be extremely baffling if the presence of neoplasm has not been considered. The sugar content was determined in 11 of the 20 patients with positive cytologic findings; in six of these it was less than 40 mg per 100 ml when concomitant blood sugar values were in excess of 75 mg per 100 ml. Thus, the cerebrospinal fluid changes in those patients often resembled the changes characteristic of a bacterial form of meningitis. The total protein content of the cerebrospinal fluid, which ranged from 30 to 400 mg per 100 ml in this series of patients, is of much less diagnostic significance than the glucose content.

In each of five of the patients the origin of the neoplasm was finally traced to the central nervous system: there were two brain stem tumors (explored but not biopsied); one medulloblastoma; one pinealoma that later disseminated into the spinal subarachnoid spaces and subsequently was controlled by radiotherapy (Figs. 6 and 7); and one anaplastic astrocytoma that eroded the wall of the lateral ventricle and disseminated into the subarachnoid spaces (confirmed at necropsy).

In two of the patients (one with malignant lymphoma and the other with terminal monocytic leukemia), the specimens of cerebrospinal fluid contained atypical cells that were interpreted as immature lymphoblastic forms. In both of these the diagnosis was finally confirmed at necropsy.

Of these 27 determinate patients, 10 eventually were studied at necropsy. In several instances it was startling to see the meager gross manifestations of the neoplasm that was responsible for the cells. Diffuse spread in the subarachnoid space may manifest itself only in the opacification of the various sulci of the brain, thus resembling meningitis (Fig. 8). Occasionally, however, nodular dural masses were observed. Other ways by which these tumor cells can gain access to the cerebrospinal fluid are the erosion of the ependymal lining of the ventricular system or invasion of the choroid plexus.

In three patients who had neoplastic cells in the specimens of cerebrospinal fluid the diagnosis was indeterminate. Unfortunately, no tissue was available for an absolute diagnosis. All three patients died at home shortly after the cytologic study was made, and necropsy was not performed. There was no previous history of neoplasm, and no neoplasm had been discovered on clinical examination.

Conclusion

The search for neoplastic cells in specimens of cerebrospinal fluid can aid in solving certain baffling clinical problems primarily referable to the central nervous system. Mental confusion, headache, nau-

sea and vomiting, associated with numbness and pain in diverse portions of the body, as well as blindness, tinnitus and vertigo may be prominent clinical symptoms. Certain laboratory findings, especially the simultaneous occurrence of a low cell count and a low glucose content in cerebrospinal fluid, should alert the physician to institute a search for exfoliated tumor cells in the cerebrospinal fluid. The procedure is not difficult but the interpretation requires care. The neoplastic cellular elements, when present, are similar to those from other areas of the body. The simplified wet-film method described is currently of great diagnostic aid in studying cerebrospinal fluid as well as other fluids of the body.

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REPORT ON THE FOURTH NATIONAL CANCER CONFERENCE

John W. Berg, M.D.

WHERE CAN I as a practicing physician hope to make the greatest gains in cancer control in the next few years? Seeking the answer to this question, some 1,600 physicians from 49 states* joined laboratory workers, biometricians and specialists in cancer therapy for the Fourth National Cancer Conference which was sponsored jointly by the American Cancer Society and the National Cancer Institute. During three very full days (three panels ran simultaneously each afternoon) on the University of Minnesota campus in Minneapolis, the dialogue that went on between basic scientists, clinicians and public health workers covered almost the entire range of current thinking in cancer etiology, diagnosis, treatment and end results.

Four years ago in Detroit, Wendell Stanley's discussion of the possible viral etiology of cancer marked a major shift in research funds and research effort. This year the trend was even further away from the idea of a foreseeable chemotherapeutic "penicillin" for cancer. Rather, the key words of this conference were PREVENTION and COOPERATION. Early in the conference, reporters asked Dr. John R. Heller, former Director of the National Cancer Institute and now President of the Memorial Sloan-Kettering Cancer Center, for his views on gains in cancer control over the next 10 years. With reasonable efforts, adequate research, and perhaps a little luck, Dr. Heller said, *preventive* measures soon should be able to reduce the present cancer death rate by 20 per cent!

The specific areas of concern with cancer as a public health problem were taken up in the panel discussion, "Cancer in the World Around Us", and in the conference keynote address by Dr. Michael B. Shimkin, Chief of the Biometry Branch of the National Cancer Institute. In addition to cigarette smoking, a reduction of which would eventually reduce lung cancer deaths by more than 20,000 per year, unnecessary X-ray therapy, industrial carcinogens, air pollutants and food contaminants all came under indictment. A frightening moment came in the panel discussion when Dr. Lester Breslow, Chief of the Division of Preventive Medical Services of the California Department of Public Health, reported a recent epidemic of liver cancer due to a change in diet. The

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**Participants also included visitors from Australia, Burma, Canada, Canal Zone, Ceylon, Chile, Denmark, England, Hong Kong, Iran, Italy, Japan, Mexico, Peru, Puerto Rico and Sweden.*

tension was eased when it was explained that the victims were fish, but the analogy remained that the dietary change had not included a known carcinogen and that the only difference expected as regards a parallel situation in man would be a slower development with longer and more widespread exposure before the danger was recognized.

Prevention of cancer, of course, is far more than a concern just of state and national bureaus. All physicians are to some extent public health physicians as they furnish much of the muscle behind preventive medicine programs. Hence the conference took pains to delineate the needs for individual effort. The most obvious point, because of the magnitude of the possible salvage involved, was that of cigarette smoking. Even the few skeptics in the audience and the larger number who had been surfeited with antitobacco data seemed startled and impressed with Dr. Shimkin's figures on age and lung cancer death rates. The younger the age when smoking was begun, the higher was the relative mortality: for those who started smoking under the age of 10 (and this was not an insignificant number) the figure was five times that for those starting after the age of 20. Dr. Shimkin pointed out that, while there was much to be said for the American right of choosing one's own poison, it was debatable whether children and teen-agers should be held capable of making such a choice rationally. Especially since cigarette advertising is particularly designed to attract the immature, it may be suggested that physicians should make comparable efforts to utilize and pass on their knowledge of the dangers of such seduction, even to setting examples (such as not smoking in hospitals) for the coming generations.

A newer concept in prevention, the high cancer risk patient, also seemed the responsibility of the individual physician. Dr. E. Cuyler Hammond, Director of Statistical Research, American Cancer Society, presented the initial findings of his massive (1,100,000 participants) six-year prospective study designated to identify high risk patients by their symptoms. The same concept was also brought into most of the panel discussions as they considered the problems of patients with excessive exposure to sunlight, with achlorhydria, with cough, with undiagnosed breast masses, with atypical cytology on cervical smears or with a history of heavy smoking. In some cases the problem is one of a proven presence of a condition known to be closely associated with cancer, such as pernicious anemia. In others it is the presence of a symptom or sign that often is due to cancer. In both situations physicians' alertness and special attention are called for, first to rule out the presence of established cancer and then to follow the patient to make sure that subsequently developing cancer is aborted in a truly early stage.

In this regard, a general consideration exemplified by the problem of cervical cytology was spotlighted by Dr. Shimkin. The value of cytology in the detection of preinvasive cervix cancer is undeniable. There is reason to believe that if every woman in this country could be studied by cytologic means every year or two, 9,000 or more of the 10,000 deaths annually from cervix cancer could be prevented. The difficulty is that though we know this, far too many physicians cannot be persuaded to use cytology routinely. (There are also theoretical limitations on the number of smears that cytology laboratories can handle, but this ceiling is rising and always has been far above actual utilization.) As long as there are women who need and want this type of protection but cannot get it from their local doctor, there will be a need and a justification for large community screening programs. The same holds true for chest X rays in male smokers and for routine examinations of the breast and oropharynx. All of these can be carried out by personal physicians, but until they are available at this level, the gap can be, will be,

must be partly filled by organized screening programs. It is the practitioner's choice if he wishes to relinquish responsibility permanently in these areas.

In regard to cancer therapy it was apparent that above the 20 per cent of cancer deaths avoidable by prevention, there is another 20 per cent that could be avoided if physicians made full, early and proper use of accepted therapies now available to them. Beyond this, much time of the panel discussions was taken up with questions that had been asked at previous conferences but had to be asked again because widely acceptable answers were still missing. Are radical mastectomy and Urban's extended radical mastectomy significantly better than simple mastectomy with or without radiation? Is surgery or radiation or a combination of these therapies the optimum treatment for early cervix or larynx cancer? Should prophylactic node dissections be done for thyroid carcinoma or melanoma? Excellent series have been presented on all sides of these questions, yet they remain matters of debate and new problems are continually being added: What hormone therapies should be used for breast and prostate cancer? What is the proper role of chemotherapeutic perfusion in cancer therapy? Is chemotherapy a useful adjuvant to primary cancer surgery? Which of the increasing number of chemotherapeutic antimetabolites and alkylating agents should be used in other treatment situations? All of these are big questions and, if the experience of the conference is any guide, to be answered adequately they require studies of some magnitude, larger than the capability of one individual or one institution. A beginning in this direction has been made by the Cancer Chemotherapy National Program, the Joint Committee for the Study of Endocrine Ablative Procedures in Disseminated Mammary Carcinoma (results reported by Dr. Ian Macdonald) and the Prostate Study Group (results reported by Dr. William W. Scott). Hopefully, as these cooperative studies prove effective in providing comparable and more useful information faster, more funds will become available and more programs will be undertaken in other fields. This is the way, and probably the only way, as Dr. Heller pointed out in an interview, that progress and achievement can be maintained in the conventional therapies while we await the vaccine against some as yet undiscovered cancer-causing virus.

Just as Dr. Shimkin began the first day's session with challenges to all groups, a note of optimism and present hope was sounded the last day in an address prepared by Dr. Herman E. Hilleboe, Commissioner of the New York State Department of Health. Discussing the care of advanced cancer patients (the "incurables") he challenged the philosophy of pessimism, neglect and abandonment. Further, he offered this observation: that, while we cannot now offer these patients complete cure of their cancers, we can *in almost every case* offer them relief of present complaints. There is almost always SHORT-TERM HOPE. Advanced cancer is no more an indication for medical nihilism than is "advanced" hypertension or "advanced" diabetes. We have the tools for true palliation and by using them we not only offer the patient months of usable life but save ourselves the shame of turning away from our "failures."

The laboratory men have their great challenge to discover the causes and cures of those diseases known collectively as cancer, but practicing physicians have almost as great and difficult a task in *applying* already gained knowledge of cancer prevention, diagnosis and treatment. If the Fourth National Cancer Conference helps them to see their opportunities and, through hope, inspires them to achievement, the assembly will have been more than successful.

The Key to an Effective Hospital Cancer Registry Program

B. Aubrey Schneider, Sc.D.

It is now more than seven years since the American College of Surgeons first announced the requirement making it ". . . mandatory that hospitals conducting cancer clinics and diagnostic clinics have as part of their program a cancer registry," and it is five years since the requirement went into effect on December 31, 1955. The latest (1960) list of cancer programs and registries approved by the College indicates that 819 institutions in the United States have met the minimum standards for classification and approval, and 82 have been designated as conducting approved cancer registries. Since, theoretically, every approved hospital cancer program now includes a cancer registry, it is apparent that, as of 1960, there will be at least 901 hospital cancer registries in the United States. On the basis of current interest in cancer registry programs, even among hospitals not attempting to fulfill the requirements for approval of a complete cancer clinical program, the total number of hospital cancer registries that have been established during the past five years may be estimated at well over 1,000.

Quantitatively, the growth in the number of cancer registries is truly phenomenal. Qualitatively, however, this rapid development of registries which have "mushroomed" throughout the country almost overnight leaves much to be desired in terms of purpose and usefulness. For example, there is abundant evidence to indicate that many of these registries have been functioning for two, three, or five years by means of the dedicated work of a secretary assigned to the job. Now, after the expenditure of a considerable amount of money, time and effort, there is no clear understanding of the purpose which the registries should be serving or the reason why they have been given special emphasis as a necessary element of an effective cancer program in the hospital.

The experience of the last five years has indicated that the effectiveness of a hospital cancer registry is not so much determined by the industry and perseverance of the secretary in charge of it as by the interest, cooperation and participation of the medical staff, and more particularly, the hospital cancer committee. Despite the College of Surgeons' first of three "Minimum Requirements for Approval of a Cancer Registry and Cancer Clinic Activities",[1] *i.e.*, a Committee on Cancer, registries have been established in some hospitals in the absence of a cancer committee. In other hospitals, registries have been established by order of the administrator, the chief of staff, the tumor clinic director, or by one or another of the department chiefs (either with or without the aim of satisfying the College's requirements for approval of a clinic program) with the result that only the most casual relationship may exist between the cancer committee, if there is one, and the registry. The latter observation was borne out by a recent survey (unpublished) in which questionnaires were directed to three different persons (the administrator, the chief of staff and the record librarian) in a group of hospitals requesting information relative to the development of a cancer registry in each institution. The lack of uniformity in the response of these three individuals to the first question, "Does your hospital have a cancer registry?", was indeed surprising and indicative of some of the problems inherent in the present understanding (or misunderstanding) and the future development of hospital cancer registry programs. This observation points up the lack of physicians' interest in (or even knowledge of)

the registry programs now in existence.

But why is professional interest and participation so essential in an effective hospital cancer registry program? Again, the experience of registry development over the past five years has indicated that in the absence of such interest and cooperation on the part of the medical staff, the registry will not be worth the time and effort devoted to it by the secretarial staff. Without the guidance of a cancer committee, hospital "tumor registries" have been set up to include *all* "tumors", *i.e.*, all etiologic entities designated by Category 8 in the STANDARD NOMENCLATURE OF DISEASES AND OPERATIONS. Such a procedure results not only in five or six times as much work as would be involved if only malignant tumors were included, but builds up a registry that encompasses a large accumulation of records that bear little, if any, relationship to the cancer problem in the institution. The volume of work may be such that follow-up is impossible, and the registry is threatened with becoming a sterile, unused, misunderstood monument to the heroic efforts of a harried and unappreciated record clerk.

When the job of establishing and maintaining a cancer registry is assigned to the clinic secretary who receives no further instruction or supervision from the medical staff, the registry is apt to include only those cases seen in clinic, either for diagnosis or follow-up. Such a program falls short of the College of Surgeons' recommendation that the registry cover ". . . every patient, private and public, inpatient and outpatient, upon whom the diagnosis of cancer is established."

If, as is found to be the case in many instances, the registry is oriented solely around pathology records, it is subject to several critical limitations. First, such a registry is likely to include only microscopically confirmed cases; for certain specific analyses, such a selection of cases is entirely desirable. However, since one of the functions of a hospital registry is to keep the staff informed about the level of diagnosis (proportion of microscopically confirmed cases) for the entire cancer case load of the institution, the registry will have no opportunity to perform one of its many useful functions if the accessions are limited only to microscopically confirmed cases. Secondly, a registry based solely on pathology records usually does not contain sufficient information on therapy or follow-up to make it of interest or use to anyone on the staff except the pathologist. The true purpose of a registry program should be that of serving *all* the physicians of the hospital staff.

Even when the registry is developed properly around the total cancer case load of the institution, there are still matters of extreme importance that demand the interest and devotion of the medical staff. Professional agreement and guidance are essential in the determination of which cases and which items of information are to be included in the registry. Medical interpretation of certain borderline diagnoses (with respect to site, type or stage of malignancy) or complicated therapeutic techniques or regimens, subject to erroneous abstracting, must be available to the registry secretary. The whole philosophy, purpose and technique of follow-up must be understood and agreed upon by the medical staff before the secretary can even attempt to institute, much less maintain, a continuing program of successful contact with all the cancer patients diagnosed and treated in the institution. To bring the registry to complete fruition through the compilation and analysis of data from the accumulated cancer records, the registry secretary will require professional guidance and supervision. Furthermore, the task of presenting the record of accomplishment to the total staff of the institution can be undertaken only by a respected colleague who is deeply interested in the cancer problem and concerned about the quality of medical care being provided the cancer patient.

Reference

1. Minimum Requirements for Approval of a Cancer Registry and Cancer Clinical Activities. In: *American College of Surgeons' Manual for Registries and Cancer Clinical Activities. 1955; p. 2.*

Letter to the Editor

[The following letter presents additional comment on the concept of biologic predeterminism which was discussed in recent issues of CA.—ED.]

In the November-December 1959 issue of *CA*, there is a summary of an essay rendered by Dr. Notkin in criticism of Dr. Ian Macdonald's concept of biologic predeterminism. Appended to this summary are Dr. Macdonald's comments concerning Dr. Notkin's views. Dr. Notkin's essay itself is a rather apologetic and completely inadequate critique of Dr. Macdonald's theory and suffers pitifully at Dr. Macdonald's refutation. Lest readers come away with the idea that there is something worthwhile in the so-called theory of biologic predeterminism, I strongly urge that my few remarks be published in the hope that they may lead to a clearer perspective on the part of all physicians dealing with cancer.

There are a lot of things we do not know about cancer.

Some cancers grow and spread rapidly, metastasizing even while the primary site is undetectable.

Some cancers reach large dimensions but are still locally confined.

Some patients seem to have an amazing resistance to cancer and others succumb quickly.

How many physicians today would disagree with these commonly heard statements? What is more to the point, how many physicians 10 years ago, or 20 years ago, or even 30 years ago would have denied the truth of any of these statements? Probably none, or only a very few whose medical degrees were acquired without benefit of basic medical studies or whose practice miraculously excluded any patients with this unfortunate disease. Insofar as our knowledge of cancer and its variabilities is concerned, what then has Dr. Macdonald contributed? Absolutely nothing. His function here has been that of a poet—he has applied words and phrases to concepts long before held by the vast majority of his colleagues but never so concisely or mellifluously worded.

"Biologic predeterminism" is indeed a neat way of saying what we all have been thinking and it even goes further because it implies some slight degree of erudition to mollify our ignorance, much in the same manner as the terms "primary" or "essential" are applied to medical conditions in preference to the term "due to unknown causes". However, it is as foolish for any physician to argue what is fundamentally meant by "biologic predeterminism" as it would be to argue what is meant by primary or essential hypertension as opposed to hypertension due to unknown causes.

It is just as useless to attack Dr. Macdonald on the grounds that he is a therapeutic nihilist, because he quickly counters that this is not at all so—that indeed he advocates surgery in many "late" cases on the grounds that such "late" tumors, although large in size, may well be tumors which are predetermined in a favorable way and which may indeed respond to surgery. He will also counter with the argument that he himself has not abandoned surgery at all and that he even applies it empirically in cases of gastric ulcer that do not respond to medical therapy within six to eight weeks when found in patients 40 years or older.

What, then, is there about Dr. Macdonald's writings and preachings that seems to so upset many other surgeons? The answer is a number of things, here listed in ascending order of importance.

1. Dr. Macdonald has repeatedly insulted his colleagues, particularly those in the field of surgery, with such remarks as the following: "The undue emphasis on early treatment ignores the complex biological nature of cancer, as well as the wide disparity of behavior of the disease

in its variable forms and sites of origin." Of course there has been emphasis on early treatment of cancer! But just how does Dr. Macdonald justify his assertion that this emphasis has been "undue"? His implication is clear—physicians emphasizing early treatment have done so *because* they have ignored the complex biological nature of cancer or have been *ignorant* of it, whereas he, Dr. Macdonald, through an astuteness and cleverness peculiarly limited to himself, has not ignored the complex biological nature of cancer or been ignorant of it! In his generosity, the good doctor would illuminate the minds of the rest of us. How absurdly officious can an individual become? The emphasis that other physicians have placed on the early recognition and early treatment of cancer is based upon the obvious and irrefutable fact that, with our current knowledge of the disease and our current armamentarium for its treatment, this is the *single factor* which we can, in some measure, control.

If Dr. Macdonald's house were aflame he would, I am sure, expect the firemen on the scene to work with the greatest urgency and dispatch to put it out. Such a fire may have begun as a small, slowly progressive one from a neglected cigarette or it may have been started by an arsonist using rags and kerosene. The progress of the fire may have been favored by the wooden structure of his frame house, or it may have been retarded by brick walls, but once the fire has begun there is only one thing within the power of the firemen —to apply the most efficient methods to stop it, and to apply them as rapidly as possible. And if Dr. Macdonald's most prized possession is hidden away in a room upstairs, he may have no way whatsoever of determining from his position on the street below whether or not that possession has yet succumbed to the flames. Unless his logic has been impaired by his smoke-filled lungs, he will urge the fire department to move with great haste on the chance that his prized possession is still intact.

What is really to the point is this question: Would Dr. Macdonald sincerely believe that the firemen hastening to the scene were unaware of the fact that their chances of putting out the blaze were dependent upon the nature of the blaze, the presence or absence of inflammable material within the house and the structure of the house and its inherent resistance to fire? Would the haste of these professional firemen indicate that they were ignorant of the different types of fires and the different types of structures subjected to this destructive force? Dr. Macdonald has propounded absolutely nothing new except the theory that his colleagues are an unfortunate lot of dull-witted, if well-meaning, physicians, as compared to himself.

2. The second objectionable aspect of Dr. Macdonald's widely publicized "theory" is his assumption that he is in some way making a positive contribution to the treatment of cancer by encouraging surgery in some cases in which there is a large primary tumor. He often refers to this in refutation of arguments advanced that he is a defeatist in his approach to surgery, for example, of cancer of the stomach. This is sheer nonsense. The vast majority of surgeons have long been well aware of the fact that such tumors do occur and have always insisted that where evidence of dissemination of the tumor cannot be found, one should always explore the area of the primary tumor for two reasons: (a) there is always the chance that it may not be a cancer but rather some other condition mimicking cancer, and (b) when the tumor has not disseminated, an attempt at cure should be made regardless of the size of the primary growth. Dr. Macdonald has not taught us these concepts. It is fatuous of him to believe that this is his personal contribution.

3. The third objectionable point in the "theory" is his oft-repeated remark that treatment of cancer, because of biologic predeterminism, should never be an emergency. Again he patronizes his colleagues. So far as I know, there have been very few cases indeed in which a physician has scheduled an operation for cancer of the stomach as an emergency procedure, let us say, in the wee hours of the morning,

as he would schedule surgery for acute appendicitis. Many surgeons do advise patients with proven or suspected malignancy to make immediate plans for hospitalization, but we are, I am sure, just as careful as Dr. Macdonald to secure a thorough and adequate work-up prior to subjecting the patient to an anesthetic and a prolonged or difficult operation. If Dr. Macdonald means that we should tell our patients that because of biologic predeterminism there is no hurry, there is no urgency, then I suggest that Dr. Macdonald spell this out for us in exact terms. Would he suggest, for example, that a patient who had planned a trip to Europe should be told to go ahead with it inasmuch as there was really no hurry because his cancer and his body had already reached an agreement as to the ultimate outcome, favorable or unfavorable? Or does Dr. Macdonald have some secret method, thus far undisclosed to the rest of us, of determining which cancer (a) is already beyond hope or cure, (b) will be as curable in six months as it is today, or (c) belongs to neither of these two categories but will reach a point that changes it from curable to incurable within a specified number of days, weeks or months?

The fact stands, and is unaltered by whatever terminology we apply to our ignorance, that we do not know which cancer is inoperable from the very beginning, or which cancer will remain curable for a long period of time. And most important of all, we cannot delineate which cancer is one that is curable now but will not be curable two weeks from now. Irrespective of how much we all are aware of the limitations of our knowledge and of the shortcomings of our treatments, we agree that surgery and irradiation are the best we have to offer and that they do save some of cancer's victims. Regardless of all the other factors involved in the curability of these cancers, there remains but one factor which *we can control* and which we must admit, in an unknown proportion of such cases, plays a part in the chances of cure—TIME. We are all aware and have long been aware, as Dr. Macdonald is, that we are desperately in need of better modalities of treatment for cancer than surgery and irradiation, but this does not alter the situation as it now stands, whether we talk of biologic predeterminism or whether we do not. It is very, very likely that when a newer and better modality is discovered for the treatment of this dread disease, TIME will remain the most important and controllable factor in its application. Only when we succeed in effecting a method of preventing cancer will TIME in the *application of treatment* of cancer become unimportant. Even then, it is quite likely that TIME will be of the essence in the application of the *methods of prevention* of cancer.

As far as I am able to determine, not one iota of improvement in the treatment of cancer has resulted from Dr. Macdonald's widely publicized, so-called theory. But if just one patient has lost the opportunity for cure as a result of the connotations implied in the words "biologic predeterminism", it is a very sad thing indeed.

—IRVING A. BEYCHOK, M.D.
Sarasota, Florida

a glance . . .

one-minute abstracts of the literature on cancer cytology . . .

Diagnosis of Lung Cancer

This paper is an analysis of the records of 100 consecutive patients with histologically confirmed lung cancer to determine the practical value of each of the diagnostic methods—bronchoscopy, scalene lymph node biopsy and cytologic examination of the sputum or bronchial secretions. In this group of patients there were twice as many neoplasms of the upper lobe as of the lower; there were nine tumors which either extended into both upper and lower lobes or were confined to main-stem bronchi. Of these patients, 84 had bronchoscopic examinations, including aspiration of bronchial secretions or washings for cytologic examination. Anterior scalene lymph node biopsies were attempted in 78 patients.

It was found that the combined cytologic studies of sputum, bronchial secretions and pleural fluid gave more positive results (76%) than did bronchoscopy and lymph node biopsy combined (60%). More than 40 per cent of the patients who had thoracotomies had positive cytologic smears as the only preoperative microscopic confirmation of the clinical diagnosis. In 63 of the patients, sputum smears were positive; in nine others they were interpreted as suspicious for malignant cells. The highest accuracy for sputum examination was obtained in the diagnosis of carcinomas in main-stem bronchi or in lower lobes, but more than one half of the upper lobe carcinomas also yielded detectable malignant cells in sputum.

Bronchoscopic examination revealed 32 positive bronchial biopsies, six visible tumors which could not be biopsied, and nine negative visual findings with positive bronchial washings. The addition of cytologic examination of bronchial washings increased the accuracy of bronchoscopic diagnosis of upper lobe lesions from 22 to 28 per cent and permitted the diagnosis of five of the peripheral tumors which were not visible through the bronchoscope. Scalene lymph node biopsy was found to be the least sensitive method of diagnosis. It provided microscopic evidence of malignancy before operation or necropsy in only two cases. When such biopsy is positive, however, it provides not only diagnostic confirmation but also a criterion of operability.

Umiker, W. O.: Diagnosis of bronchogenic carcinoma; an evaluation of pulmonary cytology, bronchoscopy and scalene node biopsy. Dis. Chest 37:82-90, Jan., 1960.

Cancer Cells in the Blood Stream

In this study 1,276 blood samples from 328 patients with malignant disease and 35 patients with various benign diseases were examined. The patients with cancer were arbitrarily classified into "curable" and "incurable" groups. The "curable" group included those patients in whom the

tumor was thought to be completely removed; the "incurable" group was comprised of patients with distant or extensive local disease. Of the 105 "curable" patients, 24 (23%) were positive for cancer cells in the circulating blood. In contrast, 73 (33%) of the 223 "incurable" patients had cancer cells in the blood stream. The percentages of positive cases were somewhat higher in blood samples obtained from veins draining the tumor (28% and 39%, respectively).

Showers of cancer cells have been isolated during operative procedures, such as dilatation and curettage of the uterus, hysterectomy, laparotomy, radical mastectomy, nephrectomy and various other excisional procedures. The presence of malignant cells in the blood stream after certain diagnostic and operative manipulation points up the necessity of avoiding or minimizing any manipulative procedure in a cancer patient which might cause malignant cells to enter the circulation.

Since no malignant cells were found in the peripheral blood stream of patients with "curable" lesions which drained into the portal system, the authors believe that the liver probably plays an important role in the destruction of cancer cells carried to it.

Long, L.; Roberts, S.; McGrath, R.; McGrew, E., and Cole, W. H.: Cancer cells in the blood stream. A.M.A. Arch. Surg. 80:639-645, April, 1960

Cancer Cells in Wound Washings

The major cause of treatment failure in clinically operable head and neck cancer has been local recurrent disease; the local recurrence rate for these lesions has been reported to range from 24 per cent to more than 50 per cent. The problem of contamination of the surgical wounds with cancer cells as a cause of failure of therapy has become of increasing interest recently with the investigation of adjuvant chemotherapy.

In this study, wound washings from 294 patients were studied over the three-year period 1956 through 1958. Of this number, 261 patients in whom radical procedures were used in operation had primary clinically operable malignant tumors with and without regional metastases and extension. In the remaining 33 patients, wound washings of benign tumors were studied. The processing of the material was by the standard Papanicolaou technique, with the smears being fixed immediately in alcohol-ether solution and stained in Harris' hematoxylin.

It was found that there were positive washings from 14 (5.3%) of the 261 malignant lesions and atypical cells from four. The tumor cells were usually found in small groups of three to five cells or as single, isolated cells. Some were found in clumps of seven to 20 cells. None of the wound washings from the 33 benign lesions was interpreted as containing cells that were either atypical or positive.

The percentage of positive washings found in this series of cases is smaller than that reported by other investigators. There appears to be a lack of correlation between the number of positive washings and the usually expected number of reported local recurrences. The findings would suggest that other factors may play a more significant role in the incidence of local recurrence in head and neck lesions.

Burke, E., and Sako, K.: Cancer cells in wound washings in head and neck surgery. Cancer 13:772-774, July-August, 1960.

Analysis of Tumor Cells in Blood

This paper presents an analysis of the size of tumor cells and cell clumps in the circulating blood of cancer patients. It was found that the average diameter of various tumor cells in both peripheral and tumor site blood was about 19 μ. The minimal diameters of malignant cells were 10 μ, and the maximal diameters were 50 μ. The average size of malignant cells in the blood and bone marrow was the same but was smaller than that of malignant cells obtained from tumor imprints in the same patient. Tumor cell clumps had average diameters of 30 μ to more than 100 μ; clumps of two to six cells were most common, but large clumps contained as many as 40 cells.

Many malignant cells are small enough

to get into the peripheral circulation without requiring the presence of arterial-venous shunts for their passage. The majority of cancer cells probably lodge and are destroyed in capillary beds since the number of cells reaching the peripheral circulation is relatively small.

The identification of malignant cells in the blood depends upon their "immature appearance" morphologically, their disproportionately large nucleolus or multiple nuclei and their atypical appearance in contrast to normal cells. Other practical techniques for identification include comparison with cancer cells in tumor imprints or bone marrow aspirates, the independent diagnosis by several observers, and a second review of all diagnoses by the same observers after varying periods of time.

Moore, G. E.; Sandberg, A. A., and Watne, A. L.: The comparative size and structure of tumor cells and clumps in the blood, bone marrow, and tumor imprints. Cancer 13:111-117, Jan.-Feb., 1960.

Incidence of Tumor Cells in Blood

Improvement in cancer therapy will require control of the dissemination or growth of blood-borne tumor emboli. This paper reports a study of the dynamics of metastasis in an attempt to correlate the presence of cancer cells in blood with the clinical and pathologic findings. The technique of isolating and identifying tumor cells in the blood utilized streptolysin for hemolysis of blood cells, filtration through a Millipore filter, and Papanicolaou staining. All patients in the study had a tissue diagnosis of cancer. Blood specimens were taken from a peripheral vein (peripheral blood) or from veins draining the tumor (local blood) at the time of operation.

Peripheral blood studies in 285 patients revealed that 79 (28%) had malignant cells in an antecubital vein. These patients were classified into early and late by the criterion of amenability to curative resection. Of 117 patients in the "resectable" group, 19 (16%) had cancer cells in the peripheral blood. Of the 168 in the "nonresectable" group, 60 (36%) had malignant cells in the peripheral blood. It was evident that as the disease progressed the frequency of cancer cells appearing in the blood increased.

Local blood specimens were analyzed in 91 patients; 39 (43%) were positive for cancer cells. Of the 75 patients with resectable tumors who had definitive surgical procedures, 30 (40%) had cancer cells in the local venous blood at operation. Of the 16 patients with nonresectable tumors, nine (56%) had cancer cells in the local blood.

It was apparent that epidermoid tumors of the cervix and of the head and neck frequently discharge cancer cells into regional veins, although clinical opinion has been that these tumors do not produce blood-borne metastases early in their course. Explanation for this disparity may lie in a biologically decreased potentiality of squamous cancer cells from these sites to produce metastatic foci either because of intrinsic cellular properties lessening their invasiveness, or because of greater host resistance to the growth of these cells Another factor is time, because the prolonged survival time today of patients with these tumors is associated with an increasing incidence of metastases found at autopsy. It seems reasonable to assume that these tumors do produce early neoplastic embolization but that, with a decreased biologic capacity to grow in the site of implantation, their metastatic foci become apparent only with prolonged periods of survival.

Potter, J. F.; Longenbaugh, G.; Chu, E.; Dillon, J.; Romsdahl, M., and Malmgren, R. A.: The relationship of tumor type and resectability to the incidence of cancer cells in blood. Surg. Gynec. & Obst. 110: 734-738, June, 1960.

The 1959 report of the Oak Ridge Institute of Nuclear Studies (Oak Ridge, Tenn.) reveals that in a study of 11 patients with leukemia it was found that large doses of total-body irradiation could produce remissions in some cases of acute disease. Twelve single-dose treatments of total-body irradiation, ranging from 200 to more than 900 r, were administered to the 11 patients. Five patients had complete or nearly complete suppression of the leukemia process; four patients showed incomplete suppression of the process, and two others died on the first posttreatment day. In most cases there was a profound fall in the white cell count in peripheral blood and in the marrow cellularity within the first four or five days. The best results were obtained with the lower doses of radiation; no prolonged survivals were seen in patients treated with more than 600 r.

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Dr. Galen M. Tice (University of Kansas Medical Center, Kansas City), in a report to the 22nd Conference of the Rocky Mountain Radiological Society held in Denver, recommended that radiation therapy for breast cancer, when used in conjunction with surgery, should be administered before the surgery rather than after it. Dr. Tice based his comments on the results of his study of preoperative radiation in 40 patients with breast cancer which was begun in 1936. In this group of patients, 55 per cent are alive five years after treatment, 35 per cent 10 years later, 28 per cent 15 years later, and 17.5 per cent 20 years later. Dr. Tice found that preoperative radiotherapy caused fibrosis in the periphery of the tumor bed which acted as a wall of resistance to the growth of the cancer and blocked its spread.

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The National Cancer Institute has published a monograph on the Proceedings of the Conference on Experimental Clinical Cancer Chemotherapy which was held in November 1959 in Washington, D. C. The monograph contains formal papers and panel discussions on important research developments in the field. The publication, NCI Monograph No. 3, is available from the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at a price of $2.00 a copy.

The Ohio State University Health Center is setting up a program of coordinated research in the cytologic detection of all forms of cancer. The project, which will be supported by grants from the National Cancer Institute for three years, is under the direction of Dr. Emmerich von Haam (Ohio State University) and Dr. Raymond F. Kaiser, Chief of Field Investigations and Demonstrations Branch of NCI. A full-time staff of three physicians and 10 cytotechnologists will be assisted by 10 faculty consultants in medicine, dentistry and allied fields.

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Reporting the results of a recent nationwide survey, the Canadian Cancer Society reveals that Canadian women appear to be more informed about breast cancer, its incidence, symptoms and possibilities of treatment, than they were six years ago when a similar survey was done. Their knowledge of other forms of cancer, however, has not made the same progress. The survey also revealed that women now have greater faith in the value of early detection and treatment of cancer. Television was cited as an important source of information on cancer.

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Congress has appropriated 560 million dollars for federal medical research activities at the National Institutes of Health for this fiscal year. General research will receive 83.9 million; cancer, 111 million; mental health, 100.9 million; heart, 86.9 million; dental health, 15.5 million; arthritis, 61.2 million; allergy, 44 million and neurology, 56.6 million. A sum of 186 million dollars has also been provided in federal grants for hospital construction.

COMING MEDICAL MEETINGS

Date 1960	Meeting	City
Oct. 6-8	American Association of Medical Clinics	New Orleans
Oct. 6-8	Central Association of Obstetricians and Gynecologists	Kansas City, Mo.
Oct. 7-9	Western Industrial Medical Association	San Francisco
Oct. 9	American Otorhinologic Society for Plastic Surgery	Chicago
Oct. 10-12	Congress on Industrial Health	Charlotte, N. C.
Oct. 10-13	Asia-Pacific Academy of Ophthalmology	Manila
Oct. 10-14	American College of Surgeons, Clinical Congress	San Francisco
Oct. 13-15	Academy of Psychosomatic Medicine	Philadelphia
Oct. 17-20	American Academy of Pediatrics	Chicago
Oct. 17-22	Symposium on Diagnosis and Treatment of Acute Radiation Sickness	Geneva
Oct. 20-22	Southwestern Medical Association	El Paso
Oct. 21-22	Symposium on "Research Approaches to Psychiatric Problems"	Galesburg, Ill.
Oct. 23-26	American College of Gastroenterology	Philadelphia
Oct. 23-27	Western Orthopedic Association	San Diego
Oct. 23-29	Pan American Congress of Gastroenterology	Santiago
Oct. 26-27	Industrial Hygiene Foundation of America	Pittsburgh
Oct. 28-29	Society of Pelvic Surgeons	Arlington, Va.
Oct. 29-30	Southern Society for Pediatric Research	Nashville
Oct. 30-Nov. 3	Southern Medical Association	St. Louis
Oct. 30-Nov. 4	American Public Health Association	San Francisco
Oct. 31-Nov. 2	Association of American Medical Colleges	Hollywood Beach, Fla.
Oct. 31-Nov. 3	Interstate Postgraduate Medical Association of North America	Pittsburgh
Nov. 4-5	Association of Clinical Scientists	Washington
Nov. 4-5	Central Society for Clinical Research	Chicago
Nov. 15-19	Puerto Rico Medical Association	Santurce
Nov. 17-20	Southern Thoracic Surgical Association	Nassau
Nov. 18-19	American Medical Writers' Association	Chicago
Dec. 1-3	Western Surgical Association	Detroit
Dec. 4-9	Radiological Society of North America	Cincinnati
Dec. 6-8	Southern Surgical Association	Boca Raton, Fla.

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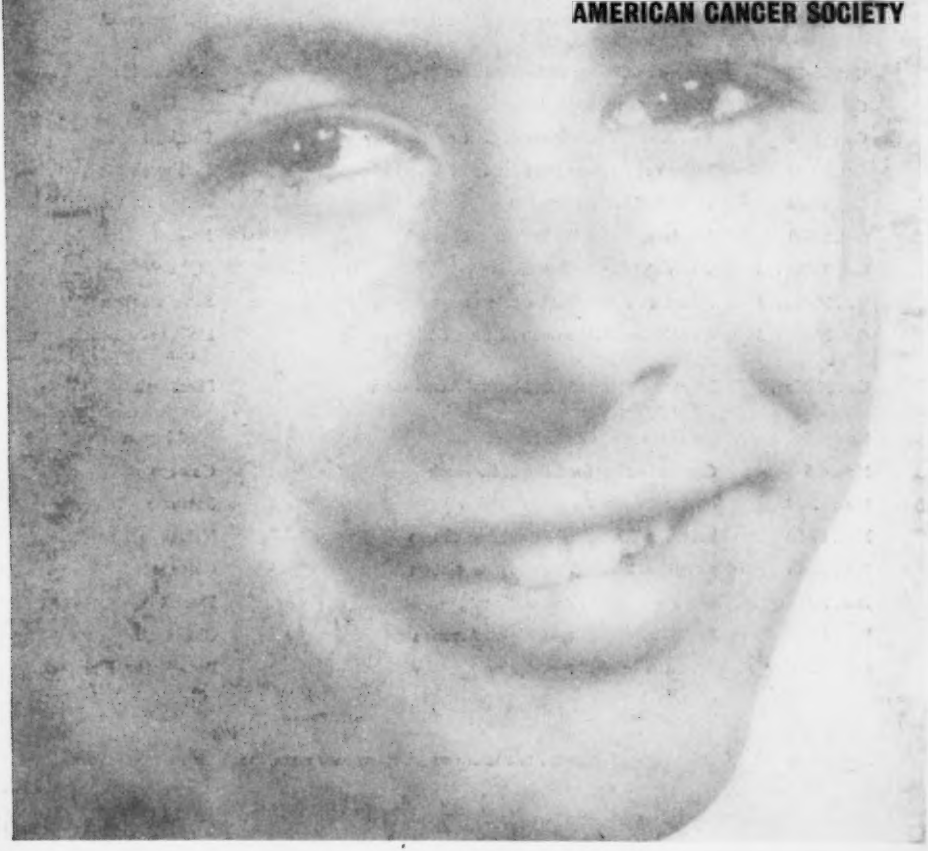
MORE THAN A MILLION AMERICAN SCHOOL CHILDREN ARE DOOMED TO EVENTUAL DEATH FROM LUNG CANCER IF PRESENT TRENDS CONTINUE. The American Public Health Association made this prediction last Fall and called upon "health authorities to undertake a broad educational effort, especially among young people, to prevent cigarette smoking."

How is this to be done, doctor? As a partial answer, the American Cancer Society has produced a filmstrip, TO SMOKE OR NOT TO SMOKE, based on a recent study of thousands of high school students. This filmstrip is available from the Society's 60 Divisions throughout the country.

The effectiveness of this educational tool will depend on the support of the entire community—teachers, parents and, most of all, physicians. Many physicians are participating in the presentation of the filmstrip.

This is another example of how the medical profession and the American Cancer Society can cooperate in essential public education in the fight against cancer.

AMERICAN CANCER SOCIETY